



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

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Who we are

- FOREUM Foundation for Research in Rheumatology is an independent fundraising institution for research funding based in Switzerland
- FOREUM is recognized by the Swiss authorities according to Swiss law and foundation regulations as a not-for-profit organization
- FOREUM is supported by EULAR, the European League Against Rheumatism.

Our mission statement

FOREUM is dedicated to promote research in rheumatic and musculoskeletal diseases (RMDs) as an independent research funding body in rheumatology. To achieve this goal, FOREUM seeks to raise funds from various donors. Basic and applied research of highest quality will be supported to reduce the burden of disease for people with RMDs.

Our principles

- 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 Europe variously afflicted by RMDs
- 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 seeks to initiate research of the highest quality oriented towards a broad range of RMDs. Only peer-reviewed research proposals that fulfil this ambition shall be considered for funding
- When developing its research strategy and grant agenda, FOREUM is interested in engaging with and learning from various stakeholders, including centres of excellence in rheumatology research and other stakeholders active in rheumatology research.

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Our 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 can 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:

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Gold



Silver



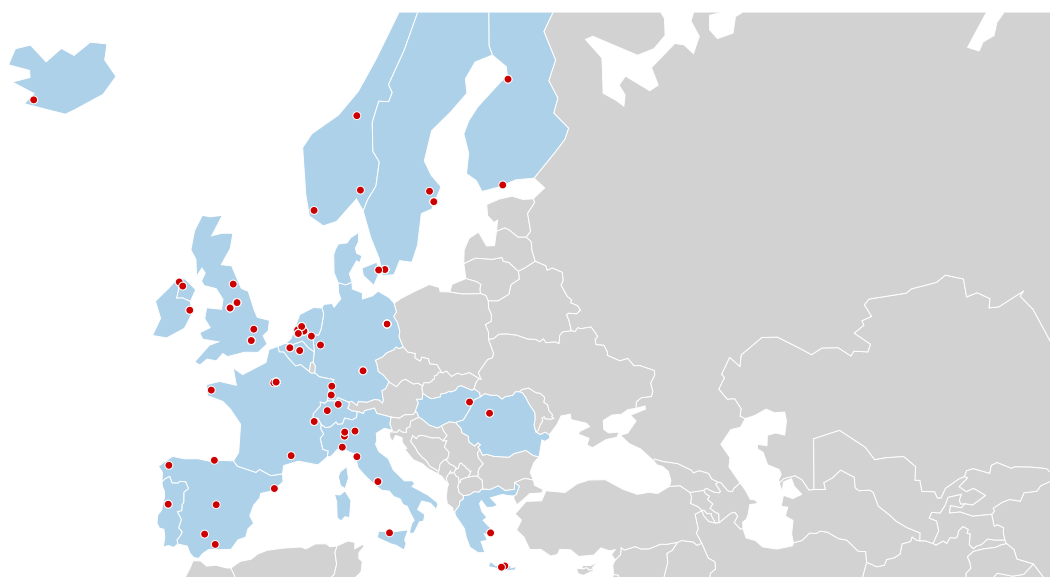
Bronze



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.

Funded science

Between 2014 and 2019, FOREUM funded 35 projects, totaling more than EUR 10 million in grants. FOREUM funded projects involve more than 100 research institutions across Europe, several networks as well as patient organisations. Research is being supported in the areas of Juvenile Idiopathic Arthritis, Comorbidities, Innovative Medicine, Myositis, Osteoarthritis, Preclinical phases of RMDs, Rheumatoid Arthritis, Registers, Spondyloarthritis and Systemic Lupus Erythematosus.



Patient organisations/groups involved

- A.M.R.E.R. Associazione Malati Reumatici Emilia Romagna
- Association France Polyarthrite, France
- Associazione Nazionale Malati Reumatici ANMAR, Rome, Italy
- Arthritis Foundation Crete, Greece
- Dutch JIA parent organisation
- European Network for Children with Arthritis ENCA
- EULAR Network of Patient Research Partners
- FER Foro Español de Pacientes
- Lupus Europe
- Myositis UK
- Stichting Bechterew in Beweging, The Netherlands

European and World Wide networks

- Pharmachild
- Biker/Jumbo
- ARTIS
- DANBIO
- NOR-DMARD
- ROB-FIN
- ICEBIO

Osteoarthritis (OA) affects a substantial proportion of the European population. Disease management is hampered by a lack of insight into the diversity of underlying OA pathophysiology and tools to stratify patients accordingly. FOREUM launched a call for research proposals in 2013 and funded this European research project.

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



Project lead

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Funding and timeline

FOREUM research grant: EUR 300.000
Project duration: 2014–2018

Publications

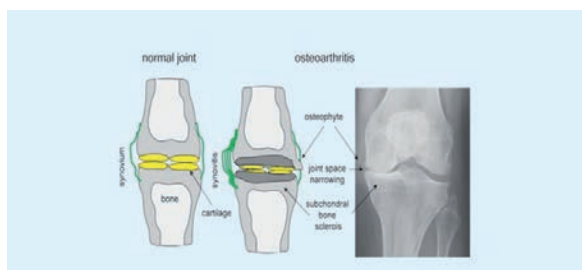
www.foreum.org/oa_1



Objectives

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

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



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.

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.

- Monteagudo S, Cornelis FMF, Aznar-Lopez C, Yibmantasiri P, Guns LA, Carmeliet P, Cailotto F, Lories RJ. DOT1L safeguards cartilage homeostasis and protects against osteoarthritis. *Nat Commun.* 2017 Jun 19;8:15889. doi: 10.1038/ncomms15889. PubMed PMID: 28627522; PubMed Central PMCID: PMC5481839.
- 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.
- 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].
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- 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.
- 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.

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Osteoarthritis (OA) affects a substantial proportion of the European population. Disease management is hampered by a lack of insight into the diversity of underlying OA pathophysiology and tools to stratify patients accordingly. FOREUM launched a call for research proposals in 2013 and funded this European research project.

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



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Funding and timeline

FOREUM research grant: EUR 300.000
Project duration: 2015–2019

Abstracts EULAR 2019

FR10518

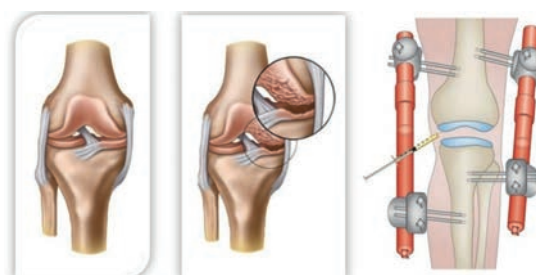
Publications

www.foreum.org/oa_2



Concept

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



Interim results

For the first time, we show that MSC number initially decline in synovial fluid (SF) upon KJD (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. This explorative study provides for the first-time data on changes in SF MSC number and their gene 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.

The fall in SF MSCs number during distraction suggests adhesion to the arthritic surfaces in the KJD environment. Further studies are necessary to unravel the processes involved.

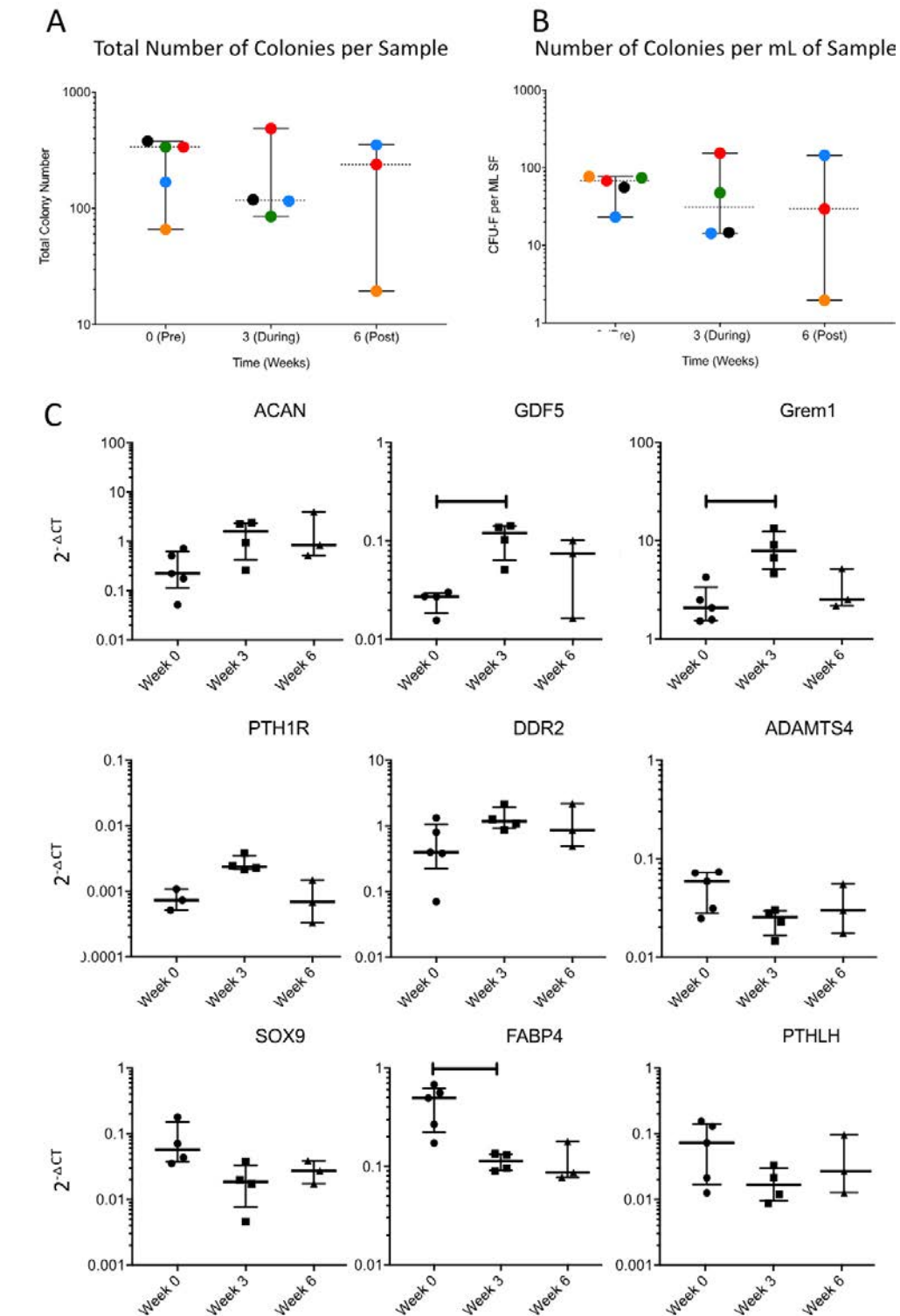


Figure 1: Changes in synovial fluid MSCs numbers and gene expressing profiles upon knee joint distraction. Bar indicates statistically significant changes (p < 0.05).

Publications

- 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 ICRS Focus Meeting December 2018, poster presentation at ORS February 2019
- Explaining the joint preservation as a result of joint distraction in clinical studies. Simon Mastbergen. Invited speaker at 5th Joint Preservation Congress at Warsaw, Poland September 2018.
- Analysis of proteins in the synovial fluid during joint distraction: unravelling mechano-sensitive pathways that drive intrinsic cartilage repair? Fiona E Watt, Benjamin Hamid, Cesar Garriga, Andrew Judge, Renata Hrusecka, Roel Custers, Floris Lafeber, Simon Mastbergen, Tonia Vincent joint last author. Oral presentation at OARSI April 2018 (abstract 15). (OAC April 2018 Volume 26, Supplement 1, Pages S17–S18).
- Intrinsic Cartilage Repair By Joint Distraction Is Triggered By a High Extracellular Matrix Turnover in Early Stages. Bedate AM, Mastbergen SC, Coeleveld K, et al. Osteoarthritis and Cartilage April 2016;24:S160-S161.

Project team/centres

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Abstracts EULAR 2019

FR10518: Longitudinal evaluation of synovial fluid and synovial fluid MSC transcript changes in subjects undergoing joint distraction

Osteoarthritis (OA) affects a substantial proportion of the European population. Disease management is hampered by a lack of insight into the diversity of underlying OA pathophysiology and tools to stratify patients accordingly. FOREUM launched a call for research proposals in 2013 and funded this European research project.

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



Project lead
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Funding and timeline
FOREUM pump prime grant: EUR 75,000
Project duration: 2015–2017

Publications
www.foreum.org/oa_3



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.

Interim 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, we 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.

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
- 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.

Project team/centres

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

Osteoarthritis (OA) affects a substantial proportion of the European population. Disease management is hampered by a lack of insight into the diversity of underlying OA pathophysiology and tools to stratify patients accordingly. FOREUM launched a call for research proposals in 2013 and funded this European research project.

Micro RNAs as biomarkers in OA



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Funding and timeline
FOREUM pump prime grant: EUR 75,000
Project duration: 2014–2016

Publications
www.foreum.org/oa_4



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.

Interim 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.

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>

Project team/centres

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Systemic Lupus Erythematosus (SLE) burdens individuals and health economies, significantly presenting a substantial unmet therapeutic need in this area. FOREUM launched a call for research proposals in 2014 and funded this European research project.

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



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

Abstracts EULAR 2019
OPo277, THU0205

Publications
www.foreum.org/sle_1



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.

Interim 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

Publications

- Bertsias G et al. Combined genetic and transcriptome analysis of patients with SLE: Distinct, targetable signatures for susceptibility and severity. ARD2019 (In Press).
- Nikolaos I Panousis, George Bertsias, Halit Ongen, Irini Gergianaki, Maria Tektonidou, Maria Trachana, Luciana Romano-Palumbo, Deborah Bielser, Cedric Howald, Cristina Pamfil, Antonis Fanouriakis, Despoina Kosmara, Argyro Repa, Prodromos Sidiropoulos, Emmanouil T Dermitzakis, Dimitrios T Boumpas. Genomic dissection of Systemic Lupus Erythematosus: Distinct Susceptibility, Activity and Severity Signatures. bioRxiv 255109; currently under review.
- Gkirtzimanaki et al. IFN α Impairs Autophagic Degradation of mtDNA Promoting Autoreactivity of SLE Monocytes in a STING-Dependent Fashion. Cell Reports 25, 921–933 (2018)
- Grigoriou M, Anastasiou M, Verginis P, Pavlidis P, Nikolaou C, Bertsias G, Boumpas D T, Banos A. Rna-seq profiling of hematopoietic stem cells in murine systemic lupus erythematosus (sle): validation and functional characterisation. Ann Rheum Dis 2017;76:A57-A58.
- Bertsias G, Panousis N, Gergianaki I, Tektonidou M, Trachana M, Pamfil C, Fanouriakis A, Dermitzakis E, Boumpas D. The genomic architecture of Systemic Lupus Erythematosus (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.
- 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.

- Bertsias G, Panousis N, Gergiannaki I, Tektonidou M, Trachana M, Banos A, Fanouriakis A, Pamfil C, Dermitzakis E, Boumpas D . Molecular characterization of SLE by RNA-Seq; Identification of genes and expression – quantitative trait loci contributing to pathogenesis, severity and tissue susceptibility Clin Exp Rheumatol. 2016; 34(4): Suppl.99: S-49.

Project team/centres

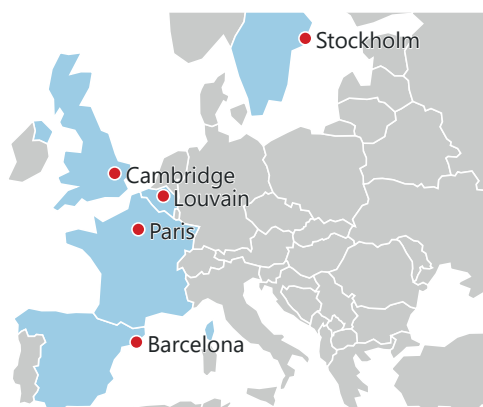
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Abstracts EULAR 2019

- OPo277: RNA sequencing and machine learning techniques predict major organ involvement in patients with Systemic Lupus Erythematosus
- THUo205: The hematopoietic stem cells (HSCs) in Systemic Lupus Erythematosus (SLE) reprogram their transcriptome: implications for the pathogenesis of the disease

Systemic Lupus Erythematosus (SLE) burdens individuals and health economies, significantly presenting a substantial unmet therapeutic need in this area. FOREUM launched a call for research proposals in 2014 and funded this European research project.

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



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Funding and timeline

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

Publications

www.foreum.org/sle_2



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.

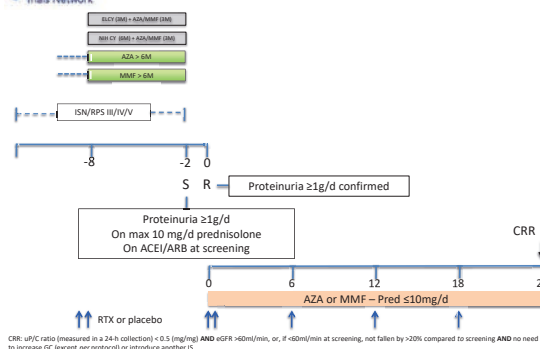
Interim results

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 healthy donors. In untreated patients, most

RING – Rituximab for lupus Nephritis with remission as a Goal

Lupus Nephritis Trials Network



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.

Conclusions

These very encouraging results showed the presence in the lupus kidney of adaptive immune cells with a differentiated and effector phenotype, associated with more severe and refractory disease.

Patient voice

We have involved Lupus Europe in the process as a patient partner organisation.

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

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- P Remy, Université Paris-Est, FRANCE
- D Mazzoni, Lupus Europe, UNITED KINGDOM

Systemic Lupus Erythematosus (SLE) burdens individuals and health economies, significantly presenting a substantial unmet therapeutic need in this area. FOREUM launched a call for research proposals in 2014 and funded this European research project.

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



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Funding and timeline

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

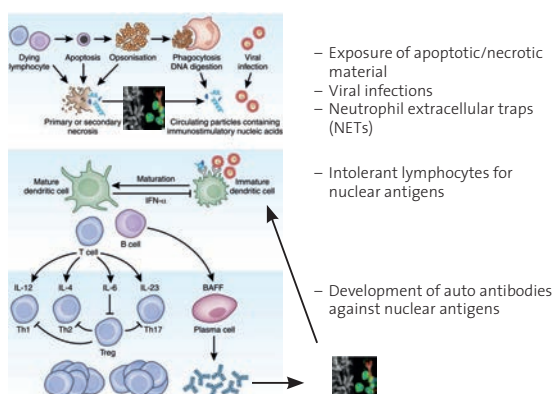
Publications

www.foreum.org/sle_3



Concept

Patients with SLE typically have circulating autoantibodies against nuclear autoantigens, such as DNA, as a result of a humoral autoimmune response. This research project intends to comprehensively study the humoral autoimmune response in SLE patients. To do so, we intend to establish an in-depth understanding of the origins of SLE-specific autoantibodies in a unique cohort of SLE patients who are treated with new biological therapies specifically targeted at the formation of autoantibodies.



Objectives

This consortium aims to investigate 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 will be 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, his-

tones, 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.

Interim results

Patients with SLE typically have circulating autoantibodies against DNA as a result of a humoral (auto-)immune response. This research project intends to comprehensively study the pathophysiology of the humoral autoimmune response in SLE patients to establish an in-depth understanding of how autoantibodies develop in a unique cohort of SLE patients who are treated with new biological therapies specifically targeted at the formation of autoantibodies. We have identified 38 refractory SLE patients with renal involvement who were treated with experimental treatment regimens (i.e. rituximab, bortezomib or combination rituximab + belimumab). We are well on our way to perform in-depth analyses in these patients which eventually will inform us if and how these novel treatments influence the formation of autoantibodies in SLE patients.

Patient voice

The experimental nature of our research proposal limits the potential contribution of patient research partners. It is however noteworthy that patient representatives are involved in the separate clinical trials at each collaborating centre which investigate therapeutic strategies that specifically target humoral autoimmunity.

Publications

- 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. FR10311 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.
- 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.
- 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.
- 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.

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

Systemic Lupus Erythematosus (SLE) burdens individuals and health economies, significantly presenting a substantial unmet therapeutic need in this area. FOREUM launched a call for research proposals in 2014 and funded this European research project.

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



Project lead
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Funding and timeline
FOREUM research grant: EUR 150,000
Project duration: 2016–2019

Publications
www.foreum.org/sle_4



Concept

Neutrophils of SLE patients have reduced ability to form reactive oxygen species (ROS), which is associated with increased disease severity and organ damage. We 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

We have previously seen that reduced ability of neutrophils to produce reactive oxygen species (ROS) is associated with increased severity and organ damage in SLE. This prompted us to ask if SLE patients are genetically predisposed to have low ROS production and how this would influence pathogenesis. We are investigating the role of NCF1 gene variants in SLE and relate this to disease phenotypes. We are also characterizing 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.

Interim results

In this project, we have identified a novel SNP in the NCF1-gene (NCF1-339), strongly associated with SLE. We have genotyped 1087 SLE patients and 1301 healthy controls and found that the low-ROS-associated T-allele is present in 11 % of patients compared to 4 % in controls (p -value = 7×10^{-20}). Patients with NCF1-339 T-dominant genotypes (T-genotypes) were diagnosed in average 6 years prior to patients with C-genotypes (p -value 2×10^{-6}).

Neutrophils of SLE patients with NCF1-339 T-genotypes had decreased ROS production and NET-release (Figure 1). NCF1-339 T-genotype is associated with high serum IFN (Figure 2) and anti-cardiolipin and anti- β 2-glycoprotein-I, autoantibodies associated with antiphospholipid syndrome (APS) (Figure 2). A significantly increased frequency of SLE patients with NCF1-339 T-genotypes had secondary APS.

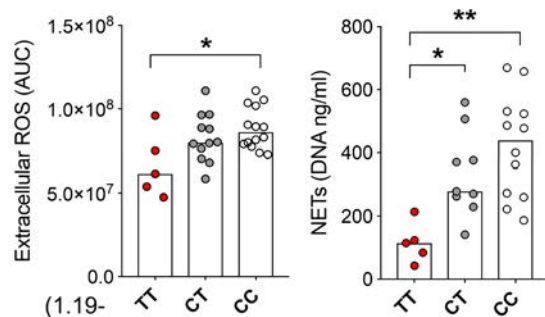


Figure 1. Extracellular ROS and NETs released of SLE neutrophils with different NCF1-339 genotypes stimulated with phorbol-myristate-acetate (PMA).

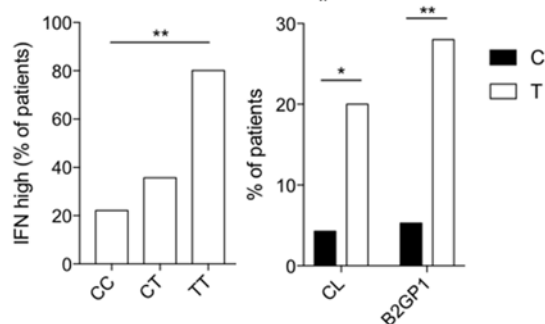


Figure 2. Serum IFN and anti-cardiolipin (CL) and anti- β 2-glycoprotein-I in SLE patients with different NCF1-339 genotypes.

Patient voice

We are since many years always working in close collaboration with patients that are also taking part in the projects, letting us be influenced by patients from their perspectives.

Publications

- Lina M Olsson, Åsa C Johansson, Birgitta Gullstrand, Andreas Jönsen, Saedis Saevardsdottir, Lars Rönblom, Dag Leonard, Jonas Wetterö, Christopher Sjöwall, Elisabet Svenungsson, Iva Gunnarsson, Anders A Bengtsson, Rikard Holmdahl. 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>. [Epub ahead of print].

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

Spondylarthropathies (SpA) comprise one of the most common of the inflammatory arthritides 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. Pathogenesis of SpA is imperfectly understood. FOREUM launched a call for research proposals in 2015 and funded this European research project.

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



Project lead

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Funding and timeline

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

Abstracts EULAR 2019

FR10360

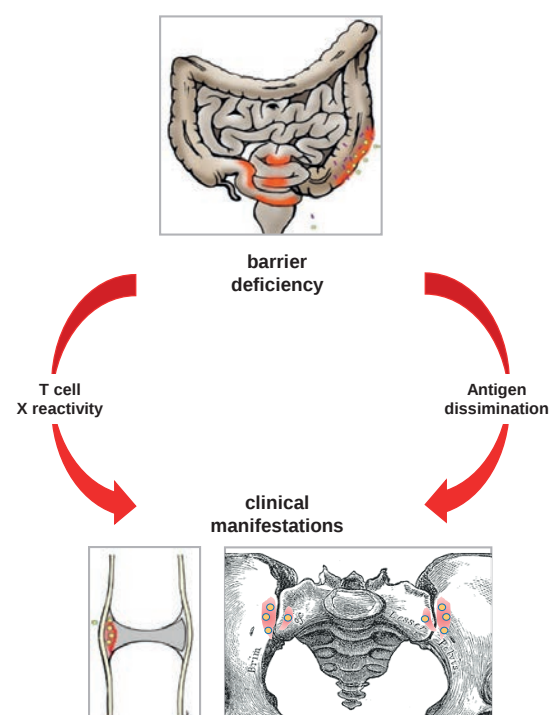
Publications

www.foreum.org/spa_1



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.

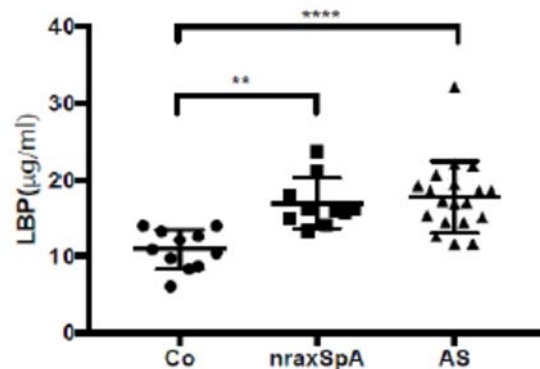


Interim results

The project started in Feb 2017.

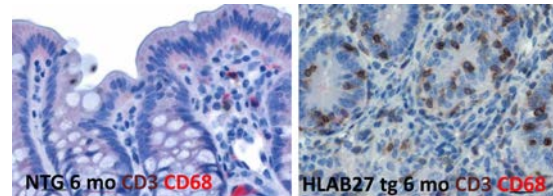
Soluble biomarkers indicative of bacterial translocation in SpA

- lipopolysaccharide binding protein (LBP) is up-regulated in axial SpA patients compared to controls.
- there is no difference between nr-axial SpA and AS and no difference between BASDAI high and 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+ monocytes 956 Affymetrix probe sets were differentially expressed between axSpA patients and HC (Berlin). Coexpression analysis with reference transcriptomes found an overlap with responses triggered by LPS and TNF and G-CFS mobilization as well as late myelopoiesis.



Mechanism of translocation in HLA-B27 tg rats

- HLAB27tg rats spontaneously develop colitis as indicted by infiltration of CD3+ T cells.
- mRNA expression data of colon epithelial cells suggest dysregulation of tight junction molecules in HLA-B27 tg rats. The differences are verified on protein level.

Patient voice

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

Project team/centres

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

Abstracts EULAR 2019

FR10360: Analysis of blood monocyte transcriptomes and bone marrow samples of patients with Axial Spondyloarthritis reveals their changes related to activation and Myelopoiesis

Spondylarthropathies (SpA) comprise one of the most common of the inflammatory arthritides 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. Pathogenesis of SpA is imperfectly understood. FOREUM launched a call for research proposals in 2015 and funded this European research project.

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



Project lead

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Funding and timeline

FOREUM research grant: EUR270.000
Project duration: 2017–2020

Abstracts EULAR 2019

THU0380, SAT0659, SAT0327

Publications

www.foreum.org/spa_2



Objectives

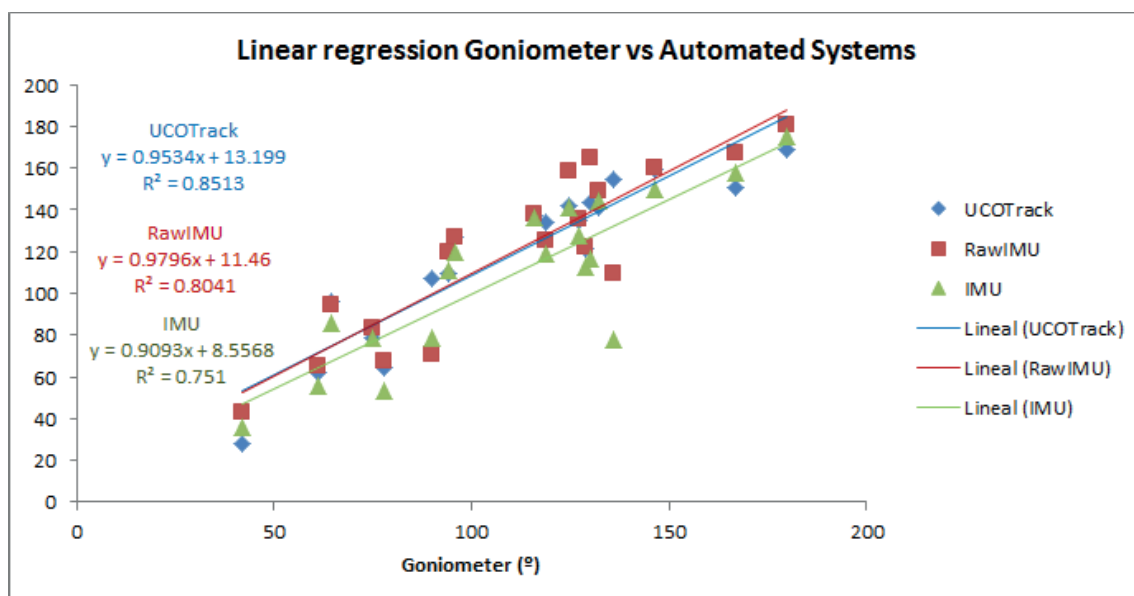
The main objective of this project is to test the reliability of electronic sensors in measuring spinal movement. Current methods rely on tape measures and are not reliable enough to evaluate new treatments for axSpa. We also want to test if we can reliably measure spinal movement when the patient is unsupervised.

To date have 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. In the next phase we will measure the responsiveness of our instrumented metrology index. We are also developing a smartphone app to allow patients to obtain feedback on their spinal mobility from wearable sensors.



Interim results

The project started in April 2017. Interim results on IMU sensor accuracy & reliability in axSpA patients will be presented in June 2019.



Patient voice

An oral communication about measuring in axSpA has been presented at the VI National Congress of Chronic Patients (Spain). Patients in Londonderry have attended a workshop to discuss the project and the design process for a smartphone application.

Publications

- Inertial motion sensors using the Vimove© System is a valid method to assess spinal mobility in patients with Axial Spondyloarthritis I. C. Aranda-Valera, J. L. Garrido-Castro, I. Martinez-Sanchez, C. Gonzalez, P. Gardiner, P. M. Machado, E. Collantes (EULAR 2018)
- Axial Spondyloarthritis posture assessment using inertial sensors J. L. Garrido-Castro, I. C. Concha-Aranda, P. Gardiner, P. M. Machado, J. Williams, E. Collantes-Estevez (EULAR 2018)
- Advanced metrology in patients with Axial Spondyloarthritis: lumbar or thoracic+lumbar measurements for spinal mobility assessment? I.C. Aranda-Valera, L. Garcia-Luque, S. Alcaraz-Clariana, J. L. Garrido-Castro, I. Martinez-Sanchez, C. Gonzalez, P. Gardiner, P. M. Machado, E. Collantes (EULAR 2018)
- Lumbar muscles stiffness in patients with Axial Spondyloarthritis is altered in comparison with healthy subjects. C. Aranda-Valera, S. Alcaraz-Clariana, L. Garcia-Luque, J. L. Garrido-Castro, I. Martinez-Sanchez, C. Gonzalez, P. Gardiner, P. M. Machado, E. Collantes on behalf of iMaxSpA Study Group (EULAR 2018)
- Validez de los sensores inerciales de movimiento utilizando el Sistema Vimove© para la evaluación de la movilidad espinal en pacientes con espondiloartritis axial. Comunicación a XLIV Congreso Nacional de la Sociedad Española de Reumatología (EULAR 2018).
- Metrología avanzada en pacientes con espondilartrosis axial: ¿medición lumbar o lumbar + torácica para la evaluación de la movilidad espinal?. Comunicación a XLIV Congreso Nacional de la Sociedad Española de Reumatología (EULAR 2018)

- El tono muscular paravertebral lumbar en pacientes con espondiloartritis axial está alterado en comparación con sujetos sanos. Comunicación a XLIV Congreso Nacional de la Sociedad Española de Reumatología (EULAR 2018).
- Evaluación de la postura espinal en pacientes con espondiloartritis axial utilizando sensores inerciales. Comunicación a XLIV Congreso Nacional de la Sociedad Española de Reumatología (EULAR 2018).
- ‘Thinking Remote’ Conference, Inverness, Scotland May 2018: Using Gamification App Design & Remote Wearable Sensors to Attain Ankylosing Spondylitis Patient’s Engagement. Mr Niall McShane, Dr Karla Muñoz Esquivel, Dr Joan Condell, Dr Philip Gardiner, Dr Juan L. Garrido-Castro
- ‘Using Gamification Design & Remote Wearable Sensors to Attain Ankylosing Spondylitis Patient’s engagement’ N. McShane, K. Munoz Esquivel, J. Condell, P. Gardiner, J L Garrido-Castro. TMED9 Transitional Medicine Conference Derry, N.Ireland 12-13 Sept 2018
- ‘Validation of a New Electronic Spinal Mobility Index for patients with Axial Spondyloarthritis Based on Inertial Motion unit (IMU) sensors’. P. Gardiner, D. Small, E. Boyle, A-M Conlon, P. M. Machado, Da Silva J.A.P, E.Collantes, J. L. Garrido-Castro* on behalf of iMaxSpA Study Group (ACR 2018)

Project team/centres

- P Gardiner, Western Health and Social Care Trust, UNITED KINGDOM (lead)
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- JL Garrido Castro, SPAIN

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- A Cuesta Vargas, Physiotherapy/ Sports Science, University of Malaga, SPAIN
- J Williams, Senior Lecturer,
- Physiotherapy/Engineering, University of Bournemouth, UNITED KINGDOM

Abstracts EULAR 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

Spondylarthropathies (SpA) comprise one of the most common of the inflammatory arthritides 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. Pathogenesis of SpA is imperfectly understood. FOREUM launched a call for research proposals in 2015 and funded this European research project.

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



Project lead

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Funding and timeline

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

Publications

www.foreum.org/spa_3



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.

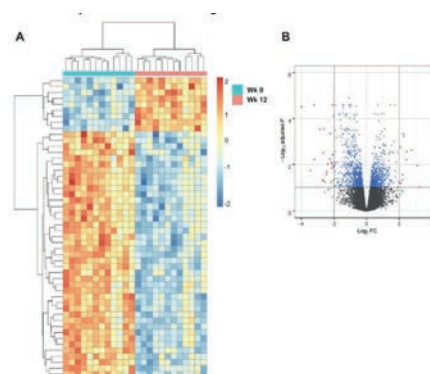


Figure 1. A. Hierarchical cluster analysis of differential expressed genes showing the log2 expression of the 100 most significantly regulated by the treatment with secukinumab genes. Normalized gene expression levels across samples are shown. B. A volcano plot. Red plots represented significant ($p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

[18 F]-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 [18 F]-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).

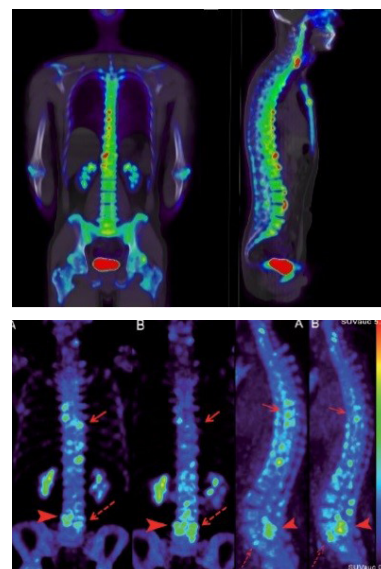


Figure 2. (A) An example of [18 F]-fluoride accumulation throughout the spine at baseline in AS patient with clinically active disease. (B) Heterogeneous effect of aTNF therapy on [18 F]-fluoride uptake

Figure 3. Baseline [18 F]-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
- 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 PSAR-TROS study. *Arthritis Res Ther*. 2018 Jul 27;20(1):153. doi: 10.1186/s13075-018-1653-5

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

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. FOREUM launched a call for research proposals in 2016 and funded this European research project to increase the utility of such databases for the wider community.

Pan-Nordic RA register network



Project lead
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Funding and timeline
FOREUM research grant: EUR 297.685
Project duration: 2017–2020

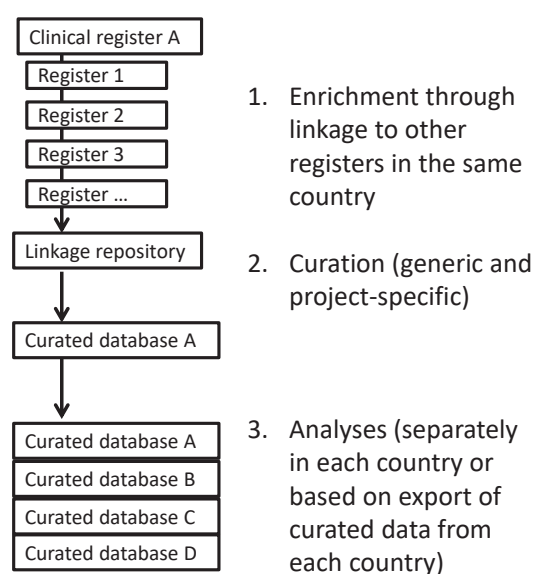
Abstracts EULAR 2019
OPo236, FR10082, FR10377, SATo365

Publications
www.foreum.org/registers_1



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.



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 Psoriatic Arthritis (PsA).

Interim results

Within the collaboration, several projects addressing specific research questions have been initiated. Whilst most of these are ongoing, some have been reported. For instance, we are investigating the use and comparative effectiveness of TNFi biosimilars, the comparative safety of non-TNFi-biologics, the use of biologics in the context of pregnancies and in patients with malignancies, and treatment outcomes following biologics use in patients with spondyloarthropathies. Several additional projects are also being launched.

Patient voice

We have established a Patient Advisory Panel that is participating in the project meetings, and influence 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 the 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.
- 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
- 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
- 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).
- 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).
- 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
- Hetland M, Østergaard M, Askling J, et al. FR10450 Commonalities and differences in data collection across european spondyloarthritis registries. *Annals of the Rheumatic Diseases* 2017;76:656-657.

- Jørgensen T, Dreyer L, Gubjörnsson B, et al. FR10518 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.
- Chatzidionysiou K, Aaltonen K, Nordström D, et al. SATo669 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.
- 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.

Project team/centres

- J Askling, Karolinska Institutet, SWEDEN (lead)
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- E Lie, Diakonhiemmet University of Oslo, NORWAY
- D Nordström, Helsinki University Central Hospital, FINLAND
- B Gudbjörnsson, University of Iceland, ICELAND

Abstracts EULAR 2019

- OPo236: Similar one-year treatment retention of originator and biosimilar Etanercept. Results of a Nordic collaboration including 1015 patients with Spondyloarthritis
- FR10082: Effectiveness of TNF inhibitors vs. non-TNF inhibitors (Abatacept, Tocilizumab and Rituximab)
- FR10377: Identical two-year treatment retention of originator and biosimilar Infliximab. Results of a Nordic collaboration including 1319 patients with Spondyloarthritis
- SATo365: 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

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. FOREUM launched a call for research proposals in 2016 and funded this European research project to increase the utility of such databases for the wider community.

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



Project lead
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Funding and timeline
FOREUM research grant: EUR 300.000
Project duration: 2017–2020

Abstracts EULAR 2019
FR0352, FR0335, SAT0271, SAT0286

Publications
www.foreum.org/registers_2



Concept

Myositis spectrum disorders (MSDs) include 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 cutaneous lesions) and lungs (Interstitial lung disease).

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

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

Objectives

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

Performed steps

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

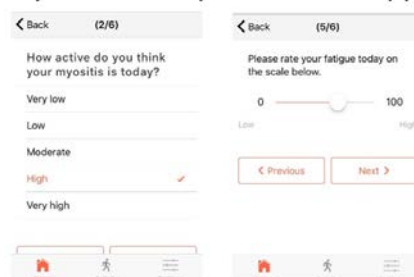
2019 Ongoing steps

- 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)
- 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)



MyoPAD smartphone-based app interface



- 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.

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

Abstracts EULAR 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

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. FOREUM launched a call for research proposals in 2016 and funded this European research project to increase the utility of such databases for the wider community.

European network of pregnancy registers in rheumatology (EuNeP)



Project lead
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Funding and timeline
FOREUM research grant: EUR 298.000
Project duration: 2017–2020

Abstracts EULAR 2019
OP0326

Publications
www.foreum.org/registers_3



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 counselling 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.



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

NTNU
Department of neuromedicine and Movement Science

Objectives

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

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. Currently, the core data set is being developed and will be published as a EULAR recommendation.

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, 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.
- Meissner Y, Strangfeld A, Costedoat-Chalumeau N, et al. FR10601 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.
- 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

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

Abstracts EULAR 2019

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

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. FOREUM launched a call for research proposals in 2016 and funded this European research project to increase the utility of such databases for the wider community.

Comorbidity in Juvenile Idiopathic Arthritis (JIA)



Project lead
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Funding and timeline
FOREUM research grant: EUR 300.000
Project duration: 2017–2020

Abstracts EULAR 2019
OP0058

Publications
www.foreum.org/registers_4



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.

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

Abstracts EULAR 2019

OP0058: Development of inflammatory bowel disease during treatment with Etanercept in patients with Juvenile Idiopathic Arthritis

There is a high interest in defining the earliest stages of Rheumatic and Musculoskeletal Diseases (RMDs). In the last years it is increasingly recognized that characteristic molecular and cellular processes antedate the clinical phases of individual RMDs. FOREUM launched a call for research proposals in 2016 and funded this European research project.

Novel treatment targets in early-stage OA



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

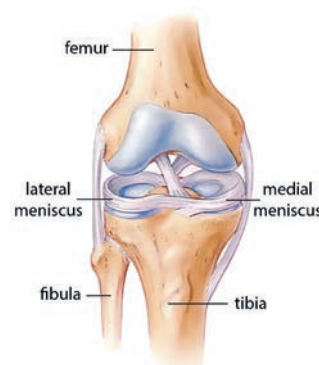
Abstracts EULAR 2019
THU0415, FRI0509

Publications
www.foreum.org/preclinical_1



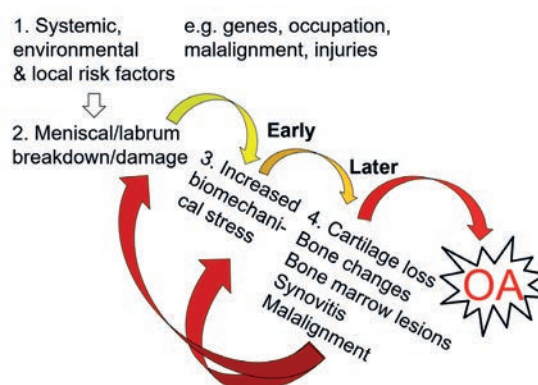
Concept

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 from patients with torn menisci (see results figure) using mass spectrometry, we will identify protein changes that accompany meniscus breakdown. We will further follow-up on a subset of these patients at risk for future OA,



using ultra high-resolution 7-Tesla magnetic resonance imaging (MRI). This technique will enable us to visualize the earliest structural features associated with OA disease progression.

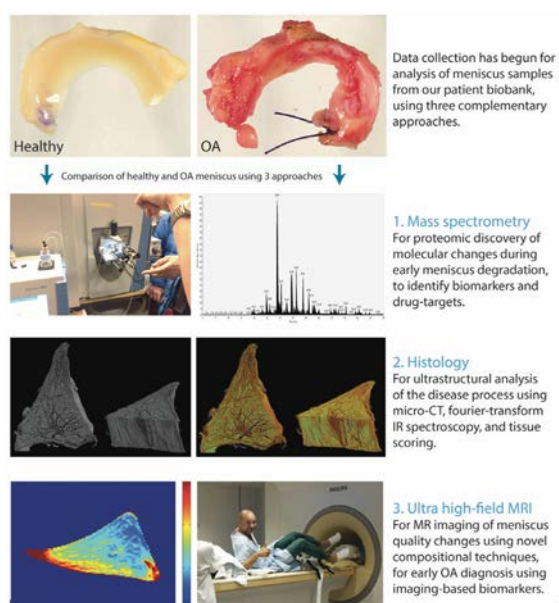
Combining our results from these two methods, we aim to pinpoint the molecular changes in the meniscus that are associated with development of OA. This will help us identify new biomarkers for early diagnosis of OA, as well as discover new targets for pharmaceutical intervention against meniscal breakdown 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, Önnérfjord P, Tjörnstrand J, Hughes HV, Englund M*, Svensson J*. *Osteoarthritis Cartilage*. 2019 Mar;27(3):476-483. *shared senior authors
- 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, Önnérfjord P. *BMC Musculoskeletal Disord*. 2018 Nov 29;19(1):416. * shared senior authors



Project team/centres

- M Englund, Lund University, SWEDEN (lead)
- P Önnérfjord, 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

Abstracts EULAR 2019

- THU0415: Exploratory protein profiling of human synovial fluid from knee osteoarthritis
- FR10509: 3D microstructure of intact and osteoarthritic human meniscus using micro-computed tomography

There is a high interest in defining the earliest stages of Rheumatic and Musculoskeletal Diseases (RMDs). In the last years it is increasingly recognized that characteristic molecular and cellular processes antedate the clinical phases of individual RMDs. FOREUM launched a call for research proposals in 2016 and funded this European research project.

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



Project lead

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Funding and timeline

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

Publications

www.foreum.org/preclinical_2



Concept

Rheumatoid arthritis (RA) is a complex disease 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 factor is 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.

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 different countries will be involved to input different view and perspectives.

Project team/centres

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

There is a high interest in defining the earliest stages of Rheumatic and Musculoskeletal Diseases (RMDs). In the last years it is increasingly recognized that characteristic molecular and cellular processes antedate the clinical phases of individual RMDs. FOREUM launched a call for research proposals in 2016 and funded this European research project.

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



Project lead

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Funding and timeline

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

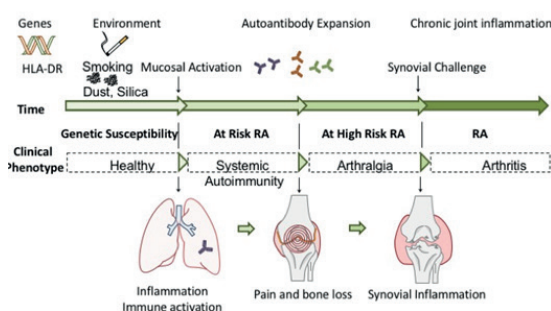
Publications

www.foreum.org/preclinical_3



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

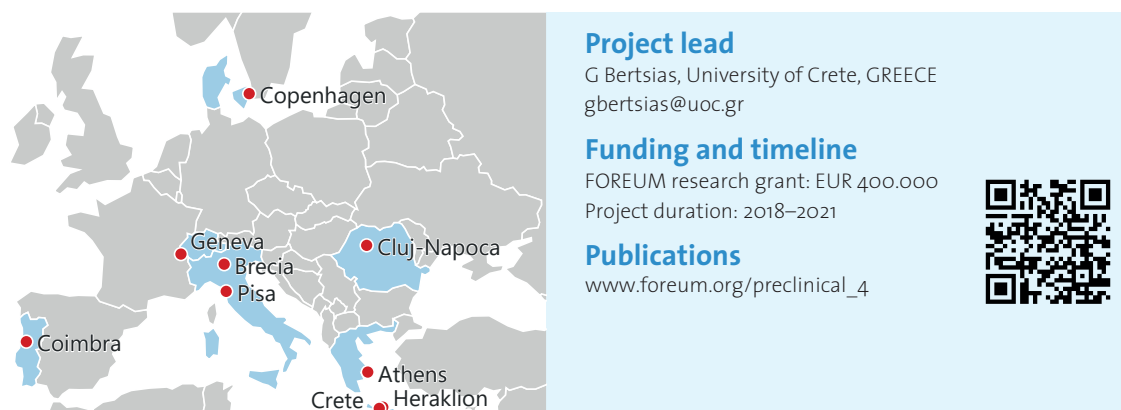
- Joshua et al. Association between number and type of different ACPA fine specificities with lung abnormalities in early, untreated rheumatoid arthritis, submitted
- Ljungberg et al. Secretory anti-citrullinated protein antibodies in serum associate with lung involvement in early rheumatoid arthritis, 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 Amsterdam, NETHERLANDS
- J Nam, University of Leeds, UNITED KINGDOM
- D Courvoisier, Hôpitaux Universitaires de Genève, SWITZERLAND

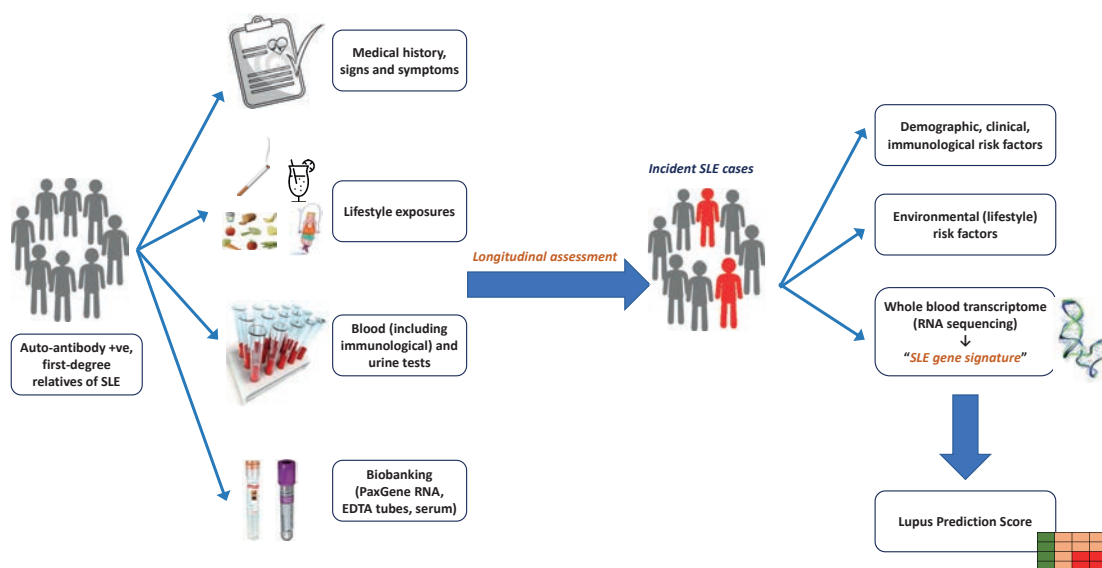
There is a high interest in defining the earliest stages of Rheumatic and Musculoskeletal Diseases (RMDs). In the last years it is increasingly recognized that characteristic molecular and cellular processes antedate the clinical phases of individual RMDs. FOREUM launched a call for research proposals in 2016 and funded this European research project.

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



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.

More than 260 individuals at-risk for SLE have already been recruited to the study (complete data and biosampling) with follow-up assessments. Incident cases of SLE have also been captured.

Patient voice

The Arthritis Foundation of Crete and Lupus 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 Bertias, 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 Dermizakis, University Hospitals of Geneva, SWITZERLAND
- A Fanouriakis, University Hospital, GREECE

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. FOREUM launched a call for research proposals in 2017 and funded this European research project.

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



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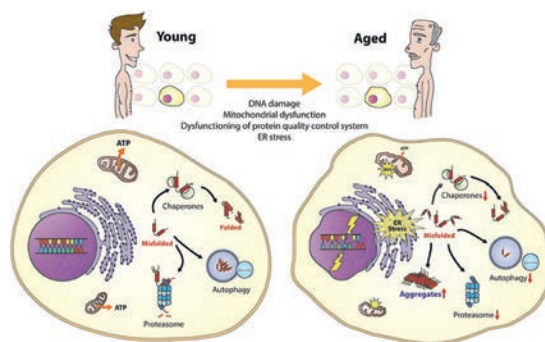
Funding and timeline
FOREUM research grant: EUR 600.000
Project duration: 2018–2021

Publications
www.foreum.org/ageing_1



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

Yassin Tachikart, Olivier Malaise, Marcus Mumme, Christian Jorgensen, Jean-Marc Brondello (2019) Seno-suppressive molecules as new therapeutic perspectives in rheumatic diseases.

DOI=10.1016/j.bcp.2019.03.017

Vinatier C, Domínguez E, Guicheux J and Caramés B (2018) Role of the Inflammation-Autophagy-Senescence Integrative Network in Osteoarthritis. Front. Physiol. 9:706. DOI=10.3389/fphys.2018.00706

Project team/centres

- D Noël, Université de Montpellier, FRANCE (lead)
- C Jorgensen, Université de Montpellier, FRANCE
- X Houard, Université Pierre et Marie Curie, FRANCE
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- 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

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. FOREUM launched a call for research proposals in 2017 and funded this European research project.

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



Project lead
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Funding and timeline
FOREUM research grant: EUR 599,881
Project duration: 2018–2021

Publications
www.foreum.org/ageing_2



Concept

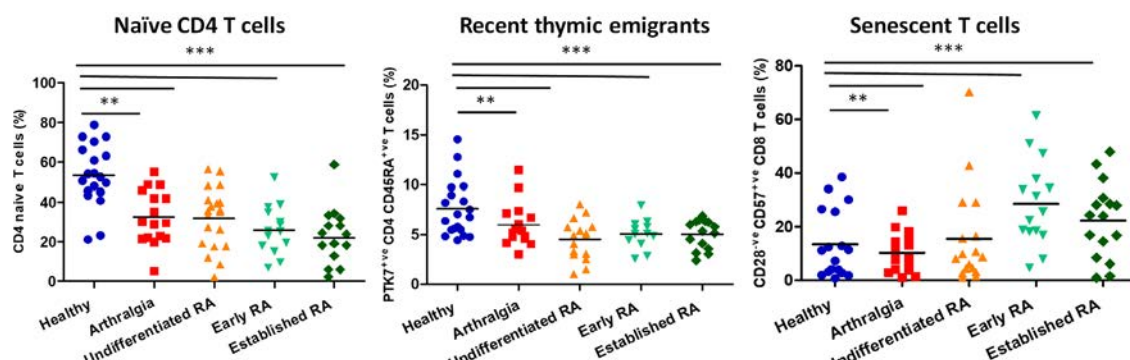
Age is a major risk factor for rheumatoid arthritis (RA), yet we understand little of the role ageing processes play in RA pathogenesis. Why this matters is that if ageing processes are a driver for RA, then improved understanding of the mechanisms involved may reveal innovative approaches to prevention 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 immunosenescence 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 occurs early in disease, but the build up of senescent cells is more likely a consequence of disease.



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.

There are no obvious risks of the project to the patient as it primarily involves the taking of a blood sample. Technical risk is minimal as the assays involved are already carried out in our laboratories.

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

Stratified medicine approaches are based on the concept that different subgroups 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. In 2017 FOREUM instigated a call for research proposal to support projects in this area.

Stratified medicine in primary Sjögren's syndrome



Project lead
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Funding and timeline
FOREUM research grant: EUR 600,000
Project duration: 2018–2021

Publications
www.foreum.org/stratified_1



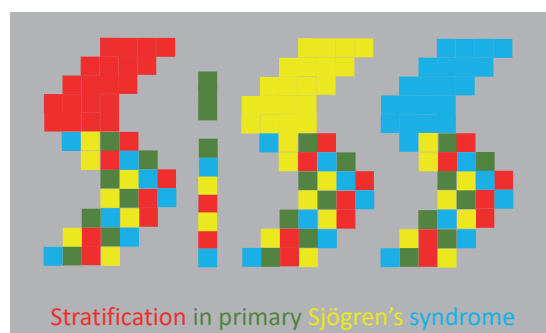
Concept

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.
- Data from historical clinical trials collated: analysis 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.

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
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- U Landegren, Uppsala University, SWEDEN
- R Omdal, Stavanger University Hospital, NORWAY
- M Bombardieri, Queen Mary University London, UNITED KINGDOM
- J Tarn, UNITED KINGDOM
- E Traianos, UNITED KINGDOM
- P McMeekin, UNITED KINGDOM
- V Macrae, UNITED KINGDOM

Stratified medicine approaches are based on the concept that different subgroups 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. In 2017 FOREUM instigated a call for research proposal to support projects in this area.

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



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

Publications
www.foreum.org/stratified_2



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.

Interim results

The project started on the 3rd December 2018.

3 patients have been recruited by the Unit of the PI at Reggio Emilia. To date only 2/6 clinical centers have received the approval by the local Ethical Committees.

Brochures about GCA and the project have been prepared with patient research partners (PRPs). RNA/DNA/proteins have been extracted from 6 TABs (retrospective cohort of patients) to check the RNA sequencing, DNA methylation and SWATH-MS profiling.

Patient voice

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

EULAR guidelines for 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

Project team/centres

- N Pipitone, Azienda Unità Sanitaria Locale, ITALY (lead)
- S Croci, Azienda Unità Sanitaria Locale, ITALY
- F Ciccio, University of Palermo, ITALY
- R Alessandro, University of Palermo, ITALY
- S Fontana, University of Palermo, ITALY
- M Gonzalez-Gay, Hospital Universitario Marqués de Valdecilla, SPAIN
- R Lopez-Meijas, 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

FOREUM International Exchange Fellowships are intended to fund excellent research projects in the field of RMDs that address any basic, translational or clinical aspect of these conditions. It is anticipated that applicants develop long-term research and clinical interest in the area of the proposal that would benefit the fellow, the home and host centers as well as the patients. FOREUM launched a call for research proposals in 2018 and funded this European fellowship project.

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



Project lead
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Funding and timeline
FOREUM research grant: EUR150.00
Project duration: 2018–2021

Abstracts EULAR 2019
OP0152

Publications
www.foreum.org/fellowship3_1



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.

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

Abstracts EULAR 2019

OP0152 : Oligoarticular Juvenile Idiopathic Arthritis does not show signs of T-cell exhaustion, in spite of increased expression of co-inhibitory receptors

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



Project lead
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Funding and timeline
FOREUM research grant: EUR150.00
Project duration: 2018–2021

Publications
www.foreum.org/fellowship3_2



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 αKG 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

TGF-activated skin fibroblasts from healthy controls and SSc patients exhibit changes in key regulatory enzymes of energy metabolism and mitochondrial dysfunction (e.g. HIF1α, PGC-1α). 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 profibrotic targets (e.g. collagen I, alpha-smooth muscle actin).

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)
- M Tomsic, University Medical Centre Ljubljana, SLOVENIA
- K Lakota, University Medical Centre Ljubljana, SLOVENIA
- O Distler, University of Zurich, SWITZERLAND
- M Frank-Bertoncelj, University of Zurich, SWITZERLAND

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



Project lead
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Funding and timeline
FOREUM research grant: EUR125,00
Project duration: 2018–2021

Publications
www.foreum.org/fellowship3_3



Concept

This multicenter, international longitudinal study will recruit JIA patients (according to ILAR classification criteria) with active disease according to JADAS 10 and 27 scoring prior starting recommended treatment. All JIA relevant data (demographics, duration, disease activity, medication usage and treatment efficacy) will be collected and parent/guardian written consent obtained.

At enrolment and during predefined scheduled follow up visits (at 3 months up to 12 months) all JIA patients will be clinically evaluated by JADAS 10 and 27 scoring, examined by ultrasound gray-scale (GS) and Power Doppler (PD) in (44 joints) using OMERACT synovitis scoring system by an expert in pediatric ultrasound.

At each visit blood samples will be obtained for evaluation of inflammatory markers (such as cytokines, chemokines and S100A8, S100A9 and S100A12). In the case of disease worsening, the same parameters will be performed as unscheduled visit.

Objectives

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

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

FOREUM Call on 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 following projects are being funded and will kick off in 2019.

Prof. Patrick Blanco (Bordeaux, France) et al: Immune mediators and metabolites to stratify Systemic Lupus Erythematosus patients at high risk of cardio vascular diseases (IMSLE)

FOREUM research grant: EUR 600.000

Project duration: 2019–2022

Accelerated atherosclerosis is an established complication of systemic lupus erythematosus (SLE), not completely explained by traditional cardiovascular (CV) risk factors, supporting the role of common mechanisms between the SLE immune dysregulation and the pathogenesis of atherosclerosis. The IMSLE (IMmunologic cardiovascular biomarkers in SLE) project aims to broadly evaluate the impact of immunologic and immune-metabolomic biomarkers over traditional risk factors and other candidate CV biomarkers in the stratification of SLE patients. This study will use the samples and data of the LBBR project and also enroll a multi-national prospective cohort of replication about 500 SLE patients. The relative importance of biomarkers will be assessed cross-sectionally at baseline using a set of serum and plasma biomarkers. Carotid ultrasonography (including carotid intima media thickness – cIMT) will serve as marker of subclinical atherosclerosis. The utility/efficacy of biomarkers over traditional risk factors will be evaluated prospectively against cIMT progression. A multi-biomarker model will be derived and validated against long-term CV events using samples and data from LBBR project. Results of this project will provide a comprehensive evaluation of clinical utility of immunologic CV biomarkers in SLE and build the basis for a CV prevention strategy that may greatly ameliorate patients' outcomes.

Prof. Weiya Zhang (Nottingham, United Kingdom) et al: Comorbidities in osteoarthritis

FOREUM research grant: EUR 600.000

Project duration: 2019–2022

Osteoarthritis (OA) is the most common arthritis and a major cause of disability in older people. However, apart from a few cross-sectional studies, little research has been done into its comorbidities. Our recent systematic review has found that 67% people with OA have other chronic diseases which is about two times more than an age and gender matched control without OA. Whether these comorbidities just co-exist with, share common risk factors, cause or are consequences of OA remains unknown. This research programme aims to examine: [1] prevalence and incidence of comorbidities in OA and time sequence between OA and comorbidities; [2] common clusters and impact of comorbidities in people with OA; [3] association between commonly used OA analgesics

and comorbidities; [4] causality between OA (or a phenotype, biomarker and risk factor of OA) and comorbidities; and [5] consistency of OA comorbidity patterns across countries. Five work packages (WP) will be performed to answer these five aims. Four national/regional registration databases in the UK, Netherlands, Sweden and Spain will be used for WP1-3. Two cohort studies (the UK Biobank and the Rotterdam study) will be used for WP4. Finally, data from different countries will be meta-analysed (WP5) for consistency between countries.

Prof. Daniel Prieto-Alhambra (Oxford, United Kingdom) et al: Characterising comorbidity in patients with rheumatoid arthritis in Europe: a multi-national federated analysis of big healthcare data

FOREUM research grant: EUR 200.000

Project duration: 2019–2021

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.

Methods:

- Data, participants: People with RA recruited to biologic registries from Czechia, Germany, Spain, Switzerland, and UK.
- Measurements: comorbidity will be characterized using 2 strategies: a) modified Charlson index (as validated in biologic registers), and b) polypharmacy.
- Processing: data will be mapped to the OMOP (Observational Medical Outcomes Partnership) common data model and curated using Achilles [<http://www.ohdsi.org/web/achilles>].

Analyses will be programmed on mapped data at Oxford. Statistical code will be shared with partners for federated analyses of the mapped datasets. Prevalence/incidence of specific comorbidities will be established. Comorbidity will be characterized as described above.

Our operational structure

Scientific Committee	Executive Committee	Board of Trustees
–Acts as advisory body for all scientific & methodological aspects	–Develops strategy on behalf of Board of Trustees –Decides on funding of peer-reviewed research proposals –Organises fundraising and manages external communication –Monitors finances	–Defines overall direction of FOREUM –Oversees strategic compliance of all activities –Approves annual financial statement
Secretariat		

Governing bodies

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

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