Annual Report 2016

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

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.
## Contents

| Preface by President of the Board of Trustees and Chairman of the Executive Committee | 2 |
| FOREUM principles and objectives | 3 |
| Current FOREUM research funding | 4 |
| Current and upcoming calls for research proposals | 13 |
| Our donors | 14 |
| FOREUM governing bodies | 15 |
| Administrative and management matters | 16 |
| Contact | 16 |
Dear colleagues and friends,

We are pleased to present the FOREUM 2016 Annual Report. From its start in 2013, FOREUM has become a consistent and reputable partner in rheumatology research funding. A key factor in achieving this has been the vision and trust shown by donors in supporting the goals and research activities of FOREUM. We are most grateful for this support and fully recognise the responsibility to translate this trust into meaningful results for the people with rheumatic Diseases with a positive impact for society as a whole.

The year 2016 has been a time of major activity and increasing operations by the foundation. We have approved funding for several new outstanding scientific research projects, we will shortly have launched two calls for research proposals on new topics; expanding the range of our research activities. Looking outwards, we are improving our visibility. We have restructured our website, and are now able to display funded research projects with the space and detail they deserve, at the same time acknowledging our donors more prominently.

We are eager to continue learning about the needs of our research community, the wishes of our donors, and the institutional requirements of our organization.

We would like to conclude with a word of thanks to all who are contributing to making FOREUM a successful and respected entity in European rheumatology research. We look forward to another year of great activity.

Respectfully,

Prof. Josef S. Smolen,  
President, Board of Trustees

Prof. Paul Emery,  
Chairman, Executive Committee
FOREUM principles and objectives

FOREUM is devoted to promote research in rheumatic and musculoskeletal diseases (RMDs) as an independent research funding body in rheumatology. It seeks to initiate research of the highest quality oriented towards a broad range of RMDs. This research should be based on collaboration between excellent centres from several countries. Only peer-reviewed research proposals that fulfil these ambitions are considered for funding.

To fulfil this goal, FOREUM seeks to raise funds from interested commercial and non-commercial donors that share its 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.

FOREUM defines its strategic goals and operations independently from other bodies. Nevertheless, the intention is to coordinate its research activities with EULAR, the European League Against Rheumatism as its initiator, in order to avoid unnecessary overlap or otherwise inefficient deployment of precious research resources.

When developing its research strategy and grant agenda, FOREUM is therefore interested in engaging with and learning from various stakeholders, including centres of excellence in rheumatology research and other stakeholders active in rheumatology research.

FOREUM allocates funds for research project funding in accordance with the priorities developed by the Scientific and the Executive Committees.

FOREUM, for the time being, only funds research proposals submitted by way of an official call for proposals as regularly issued by FOREUM. Projects submitted to FOREUM individually and outside an official call cannot be considered. Members of FOREUM bodies and the EULAR Executive Committee are excluded from participating in research project applications.
FOREUM funded 15 projects, totalling more than EUR 3.8 million in grants. In these projects more than 30 research institutions across Europe, several networks as well as patient organisations. Research is being supported in the areas of Osteoarthritis, Systemic Lupus Erythematosis, Spondyloarthritis and Registers.

Projects funded under the Osteoarthritis call

Osteoarthritis (OA) affects a substantial proportion of the European population. The OA burden in terms of individuals and health economies will likely be rising in coming years due to ageing and increased prevalence of obesity. The aetiology of OA is complex as is the involved multi-tissue pathology. Risk factors for OA onset and progression differ between anatomical sites, with most research focusing on the knee. FOREUM launched a call for research proposals in 2013 and funded the following European research projects.

Prof. Rik Lories et al: Pro-resolving mediators in osteoarthritis: homeostatic signals in the joint organ?

Osteoarthritis (OA) is characterized by a progressive loss of tissue homeostasis leading to structural damage in the whole joint. Inflammation is a key component of OA in a large number of patients and a clear therapeutic target. The applicants hypothesize that inflammation in OA is sustained by a lack of pro-resolving molecules. The characterization of poly-unsaturated fatty acid metabolites as specialized pro-resolving mediators (SPM) has opened new directions for research.


Prof. Floris Lafeber et al, Netherlands: Intrinsic regeneration of osteoarthritic cartilage by unloading involves peri-articular stem cell activity: a joint effort

“Spontaneous” cartilage repair is recognized in animal models, and more recently impressive proof of concept for “spontaneous” cartilage repair following joint distraction in man has been furnished. It is likely that joint fluid and nearby resident stem cells are key to this hitherto poorly understood biological process. The collaborative group will delineate the unknown mechanisms by which mesenchymal...
stem cells (MSCs) in the context of the intra-articular milieu are involved in this repair activity and how their role can be optimized. The project aims to unravel the still unknown mechanisms that lead to cartilage repair and reveal the mechanisms by which MSCs are involved in this repair activity and how their role can be optimized. Acquiring this knowledge will cross new frontiers to establish actual treatment of a still incurable joint disease.

**Prof. Philip Conaghan et al: PEARL OA - Partnership for EARLy knee OsteoArthritis definition through imaging and tissue biomarkers**

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

The results of this work will inform further studies to explore the relationship of bone to OA development and progression, funded through a large collaborative European grant. On the basis of the 3D imaging biomarkers evolved through this grant, the applicants are 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.


**Dr. Ingrid Meulenbelt et al: Micro RNAs as biomarkers in OA**

Up until now strikingly little progress has been made in the development of disease modifying osteoarthritis (OA) drugs. Lack of insight into the diversity of underlying OA pathophysiology and absence of tools to stratify patients based on required mode of action have likely contributed to the diminished progress. For that matter, the pump and prime project “Micro RNAs as Biomarkers in Osteoarthritis” encouraged exploration of a potential new biomarkers source being micro RNAs (miRNA). miRNAs
are small RNA molecules regulating (disease) processes in tissues. Unique is the fact that miRNAs can be secreted as messenger from tissues into the circulation where they were found to reflect ongoing (pathophysiological) conditions. The project team was able to establish isolation of miRNAs from relative small amount of plasma (100 μL) that was of excellent quality and quantity for next generation RNA-sequencing and RT-qPCR. As such significant differences in circulating miRNAs between OA cases and controls were identified.

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 and thus potentially enhance clinical trial development in the near future. The current approach is incorporated in a pending H2020 grant application.

Projects funded under the Systemic Lupus Erythematosus call

Systemic Lupus Erythematosus (SLE) affects people across the European population. The SLE burden in terms of individuals and health economies remains significant in the absence of sufficient highly effective therapeutics, predictive biomarkers and optimized treatment strategies. The call, launched in November 2014, initiated 30 letters of intent from around Europe of which eight were invited to submit full applications. Four projects were finally selected for funding. Research grants were awarded to the following teams who have started their research in between 2015 and early 2016.


Several types of cells are involved in SLE including lymphocytes, monocytes, neutrophils and endothelial cells, all of which originate from hematopoietic stem cells. RNA-seq (RNA Sequencing), is a technology that reveals a snapshot of RNA presence and quantity from an individual genome at a given moment in time. The applicants have used this technique 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 such as disease in the brain or in the kidneys. It is planned to use this technique to interrogate the cells in the bone marrow (stem cells) to identify targets for new therapies.
Publications:


Prof. Frédéric A. Houssiau et al: REFRACT - Refractory lupus nephritis: a tissue-based pathophysiological approach performed within the frame of RING, a clinical trial designed to test the efficacy of rituximab.

Lupus nephritis (LN) remains a severe complication of SLE, impacting long-term survival and quality of life. In order to test the efficacy of rituximab (RTX) in this niche indication, an investigator-initiated trial, entitled RING, was designed. REFRACT is a RING sub-study in which baseline and 6-month repeat renal biopsy will be performed. Cells infiltrating the kidneys, especially B-cells responsible for autoantibody production, will be scrutinized (flow cytometry, transcriptome, cloning, etc.), in order to unravel the mechanisms underlying refractoriness. One of the hypothesis 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 B-cell stimulation. It is hypothesized that the study of paired repeat renal biopsy samples, after RTX or SOC, will allow the applicants to unmask the mechanisms of action of RTX.

Dr. Y.K. Onno Teng et al: NET-ting the autoreactive B cell memory by therapeutically targeting the humoral autoimmunity in patients with systemic lupus erythematosus

Patients with systemic lupus erythematosus (SLE) typically have circulating autoantibodies against DNA. These autoantibodies are produced by plasma cells, which develop from autoreactive B-cells as a result of a humoral (auto-)immune response. Classically, a humoral immune response encompasses three pivotal steps: a) the
response is triggered by an (auto-) antigen. In the case of SLE patients this is extracellular DNA or other nuclear material; b) as part of the humoral response a memory pool of B-cells is formed, including autoreactive B-cells in SLE patients; and c) B-cells are triggered to develop into plasma cells producing antibodies, including anti-DNA autoantibodies. The research project intends to comprehensively investigate all three components of the humoral autoimmune response in SLE patients treated with B-cell and plasma cell targeted therapies.

Prof. Anders A. Bengtsson et al: Deciphering the role of ROS and neutrophils in the SLE pathogenesis

Patients with systemic lupus erythematosus (SLE), an autoimmune rheumatic disorder, frequently have uncontrolled chronic low-grade inflammation leading to irreversible organ damage and also shortened life-span despite all new therapies that are available today. Thus, there is a great unmet need for early identification and prediction of disease activity to decrease inflammation. In this project we will in detail characterize the role of neutrophils, our most abundant white blood cell in SLE. One very important feature of neutrophils is to generate reactive oxygen species (ROS) to kill bacteria, but it is now known that ROS also have effects on the immune system. We think that neutrophils might be very important in how the immune system is misdirected in SLE and we will therefore investigate effects of ROS on some of the most well-known dysregulated processes we know in SLE. This increased understanding of how neutrophils are involved in SLE will also be used to develop biomarkers which will be used to predict and monitor the disease.

Projects funded under the Spondyloarthritis call

Spondyloarthritis (SpA) comprise one of the most common of the inflammatory arthritidies in Europe, and consist of a spectrum of inflammatory diseases that affect primarily the peripheral joints and spine but can also involve other tissues like skin, gut and eyes. As such, SpA can mediate a substantial impact on those affected. Pathogenesis of SpA is imperfectly understood. Current available treatments and assessment tools that we have to aid therapeutics have improved markedly in recent years, but for a significant number of patients they remain inadequate. There are still too few studies that inform the best strategy for treatment, few or no effective biomarkers exist to stratify treatment and the health economic and personal impact of some of these diseases is not well defined.

The call for proposals, launched in summer 2015, initiated 16 letters of intent. Seven have been invited for full applications. The following researchers and their teams made the cut in the thorough evaluation process and have been awarded a FOREUM research grant. These projects will start their research in 2016.
Dr. Uta Syrbe et al: Role of gut bacteria in the pathogenesis of Spondyloarthritis (SpA)

Spondyloarthritis comprises a group of diseases which are characterized by inflammation within peripheral joints and/or the spine. It is known that the genetic background contributes to disease development, but it is still unclear what causes the activation of immune cells in these genetically predisposed people leading to inflammation within the joints and the spine. Studies in patients with spondyloarthritis showed that about 5-8% also suffer from overt inflammatory bowel disease associated with diarrhea and abdominal pain. Moreover, also about 50% of spondyloarthritis patients without clinical signs of inflammatory bowel disease have mild inflammation within the gut, which is only visible by microscopic investigation. The gut harbors a realm of bacteria which are prevented from entry into the body by multiple mechanisms constituting the intestinal barrier. Upon inflammation – this barrier might be impaired and bacterial components may cross the gut and directly or indirectly activate immune cells either within the gut but also at distant regions of the body such as joints or spine. Therefore, the team wants to analyze if the natural barrier function of the gut is disturbed in spondyloarthritis and if an aberrant load of bacterial components enters the body in these patients. This will be investigated by analysis of serum and gut samples from spondyloarthritis patients. Moreover, an experimental rat model which resembles many facets of the human disease including joint inflammation and gut inflammation will be used. Understanding these pathogenetic relations may identify new treatment targets and is the basis for a curative treatment of the disease.

Prof. Nataliya Yeremenko et al: Mechanistic studies of IL-17 versus TNF blockade in spondyloarthritis (SpA)

Anti-TNF is a powerful treatment for patients with spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis. Anti-TNF, however, is not effective for all aspects of disease (for example: it does not halt ankylosis) and for all patients. Anti-IL17A, recently approved by EMA, is now appearing as a second good treatment option for patients with spondyloarthritis. What is not known, however, is which patient or which disease manifestation will benefit most from treatment with one versus the other biologic drug. A first step towards ‘tailored’ treatment is to understand better which cellular and molecular processes involved in the disease are differentially modulated by one versus the other treatment. This ‘biologic’ profile could then be matched to a specific patient subset, which would optimally benefit from the treatment with either anti-TNF or anti-IL17A. In other words: understanding how exactly these two powerful treatments work is a first but crucial step to determine who should benefit most from the treatment.
Dr. Philip Gardiner et al: Can Inertial Movement Sensors (IMUs) provide a valid and reliable way of measuring Spinal Mobility in Axial Spondyloarthritis (axSpa): a Clinimetric Evaluation

With recent advances in the accuracy of ‘wearable sensors’ they are now widely used in mobile phones, watches and other wearable devices. This technology has been tried in patients with low back pain but has not yet been used in patients with AS. The standard method of measuring spinal mobility using a tape measure is known as the Bath AS Metrology Index (BASMI). Unfortunately, it is not accurate enough to evaluate new treatments for AS and it cannot be used in the home setting. Another ‘motion-tracking’ method uses a set of cameras to measure movement accurately. Tests with one of these setups (UCOTrack) showed that it was more accurate and reliable than BASMI, and it was also better able to show changes with treatment. MRI scans of the spine can detect changes in inflammation before and after treatment but again this is too expensive to be widely used. Previous studies showed that changes in the BASMI didn’t match the changes seen on MRI, so part of this study will be to compare the MRI changes with changes in the ‘sensor mobility index’ (it is called IMU-ASMI for now).

Projects funded under the Registers call

There is increasing interest in providing the maximal benefit for the Rheumatic and Musculoskeletal Diseases (RMD) community from the extraordinary resources contained in the large clinical registers that have been gathered over recent decades. FOREUM initiated a call for research proposals, with the objective to increase the utility of such databases for the wider community. The call, launched in January 2015, initiated 19 letters of intent from around Europe of which seven were invited to submit full applications. Four projects were finally selected for funding. Research grants were awarded to the following teams who start their research in 2017.

Prof. Johan Askling et al. A pan-Nordic Rheumatology Register network

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. For this, study protocols and the raw data in each register need to be harmonized such that each register asks exactly the same question and treats its data similarly.
The Nordic countries have similar health-care systems and other national registers (on malignancies, sick-leave, et cetera) that can be linked together. ARTIS (Sweden), DANBIO (Denmark), NOR-DMARD (Norway), ROB-FIN (Finland) and ICEBIO (Iceland) represent some of the largest registers of inflammatory arthritis and their biological therapies.

**Our objectives are**

- To establish a standing network across the five Nordic Rheumatology registers, which will create the largest and most versatile system of Rheumatology registers worldwide
- To use this harmonized approach for studies of clinical questions in Rheumatoid Arthritis (RA), Spondyloarthropathies (AS/SpA), and Psoriatic Arthritis (PsA).

**Dr. Lorenzo Cavagna and Dr. Hector Chinoy et al: IMPROVEMENT - Improving the outcome in myositis spectrum diseases: core set variables harmonization and use from children to adulthood**

Myositis is an inflammation of the muscles that causes weakness. Patients affected by myositis often cope with additional major health problems related to myositis, such as disease of the lungs, joints and skin, hence the term “myositis spectrum disorders” (MSD). The onset of myositis and MSD can be very variable and be very difficult to diagnose – such as when patients lack obvious muscle involvement, and may have other features to start off with such as arthritis or lung disease, so the risk of making the wrong diagnosis can be high. The myositis expert community recognises that we have much to learn and to teach about the different ways the diseases present (in adulthood and in childhood), the blood tests related to the diagnoses and the best treatment options to improve survival and increase quality of life, with special attention to the vulnerable period of chronic illness when the teenage patient is transitioning to an adult patient.

**Our aim is**

To harmonize the international registries with MSD: EUMYONET and AENAS with national registries and hospital records to create a longitudinal database to improve follow up of patients and to improve treatment and outcome of disease.
Anita Strangfeld, MD, Rebecca Fischer-Betz, MD, PhD et al: European Network of Pregnancy Registers in Rheumatology (EuNeP)

The goal for all people with inflammatory rheumatic disease (IRD) is to live a normal life without limitation in daily life. This includes family planning and having children. There is a high unmet need of robust data on the outcomes of pregnancies and on the safety of a substantial number of drugs when used before or during pregnancy. The aim of our project is to combine existing data and to improve future pregnancy counseling by using better information on pregnancy outcomes and drug safety. Experts in Europe who already run prospective pregnancy registers in women with IRD will be brought together to evaluate the nature and extent of existing data as well as the methods of data collection and to identify gaps and drawbacks for joint data analyses.

Our objectives are

- To bring together experts who already run pregnancy registers in Europe
- To evaluate the nature and extent of existing data and the methods of data collection
- The definition of a common core data set as primary outcome
- To develop methodological approaches for joint data analysis
- To perform a first joint data analysis and publication on pregnancy outcomes as secondary outcome
- To enable newly set-up pregnancy registers to use the methods and approaches already developed

Prof. Nico Wulffraat et al: Comorbidity in Juvenile Idiopathic Arthritis

Comorbidity can be defined as the presence of 2 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. 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.
FOREUM call for research proposals on Preclinical phases of RMDs

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

A call for research proposals in the area of Preclinical phases in rheumatic and musculoskeletal diseases has been launched in the summer of 2016. The call initiated 20 letters of intent. Results will be published online in summer 2017 on www.foreum.org.

Current and upcoming FOREUM calls for research proposals

Thanks to already committed donations for the coming years, FOREUM will be able to issue further calls for research proposals in the coming six to twelve months and fund successful projects.

Currently a call on Ageing in RMDs is in evaluation; results will be announced in July 2017.

In the first half of 2017 a call on Stratified medicines in rheumatology will be launched.

Topic suggestions were ranked and evaluated by the FOREUM Scientific Committee, which then made a final topic recommendation to the FOREUM Executive Committee and Board of Trustees.
In 2016 FOREUM has received donations or confirmation of financial support from various donors. The FOREUM leadership has the pleasure to express gratitude to the following supporters:

### Platinum

- abbvie
- AstraZeneca
- Lilly
- eular
- Pfizer

### Gold

- Roche

### Silver

- Novartis Pharmaceuticals

### Bronze

- Samsung
- SAMSUNG BIOEPIS

### Donors

- gsk
- MSD
Governing bodies and members (from June 2016)

Board of Trustees

President: Prof. Josef S. Smolen, Austria

Co-President: Prof. Steffen Gay, Switzerland

Prof. Ferdinand C. Breedveld, Netherlands

Prof. Maxime Dougados, France

Mr. Heinz Marchesi, Switzerland

Executive Committee

Chairman: Prof. Paul Emery, UK

Treasurer: Prof. Jiri Vencovsky, Czech Republic

Dr. Daniel Aletaha, Austria

Prof. Carina Boström, Sweden

Prof. Christopher Denton, UK

Prof. Angelo Ravelli, Italy

Mrs Diana Skingle, UK

Non-voting members:

EULAR President: Prof. Gerd Burmester
Board of Trustees members
Chairman Scientific Committee

Scientific Committee

Chairman: Prof. Georg Schett, Germany

Prof. Francis Berenbaum, France

Prof. Dimitrios Boumpas, Greece

Dr. Loreto Carmona, Spain

Mr. Marios Kouloumas, Cyprus

Dr. Caroline Ospelt, Switzerland

Prof. Carlo Salvarani, Italy

Dr. Michaela Stoffer, Austria

Prof. Lucy Wedderburn, UK
FOREUM continues to increase the in organizational capacities. In 2016, the foundation established a 60-percent administrative position at its secretariat dedicated to supporting the FOREUM committees in their work, managing the research grant agreements, maintaining regular contact with our donors, and dealing with legal matters as requested by the Swiss supervisory authorities. Thanks to FOREUM’s good relations with EULAR, the European League Against Rheumatism, it can currently draw on some of EULAR’s infrastructure and expertise in managing an international scientific charity organization. FOREUM seeks to expand its administrative capacities over time in line with its growing research activities and managerial needs. The goal, however, is to keep administrative expenses as low as possible; in 2016, administrative expenses accounted for less than 3 percent of the overall donation income.

Contact

For regular information on current and future activities of FOREUM, please visit our website or write to the FOREUM Secretariat.

FOREUM Foundation for Research in Rheumatology
Secretariat
Seestrasse 240
8802 Kilchberg
Switzerland

Phone: +41 43 311 55 66
info@foreum.org
www.foreum.org