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Dear colleagues and friends,

We are pleased to offer you the FOREUM 2015 Annual Report. In its second formal reporting year FOREUM has again made significant advances in all aspects of our organization. One facet of the foundation that exceeded our expectations is the great interest shown by the pharmaceutical industry in supporting the goals and research activities of FOREUM. We recognize this support with great esteem and also as an obligation towards our partners.

The year 2015 has been a time of major activity by the foundation: We have approved for funding a fair number of new research projects, we have launched or prepared two new calls for research proposals on topics that are expanding the range of our research activities. Institutionally, too, FOREUM has been an organization in progress: We have worked on refining our administrative and managerial processes keeping in mind that all our scientific experts and members of our leadership groups are working on an honorary basis. And as we are collaboratively working with researchers and donors, we are learning more 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 will define its strategic goals and operations independently from other bodies. Nevertheless, the intention is that it will 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 are excluded from taking a leading role in research project applications.
In 2013 FOREUM started its research funding activities with a call for proposals on the topic of osteoarthritis; two full projects were funded and two received pump prime financial support. In late 2014, a call for project proposals on systemic lupus erythematosus was launched, resulting in four projects being funded. A third call on spondyloarthritis followed in summer 2015, with three projects funded.

The projects funded by FOREUM under this call are currently performing their research. Our agreements with grant recipients require reporting on the progress at regular intervals; progress reports will be submitted to the FOREUM Scientific Committee for review. Grant payments are subject to positive review of the progress reported.

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.

(1) Prof. Rik Lories et al, Belgium: 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. The applicants’ preliminary data suggest that some SPM are present in the synovial fluid. They aim to further understand their roles in OA using a systematic approach to document their presence in OA patients and their effects on key processes involved in joint development, homeostasis and disease. Analysis of these SPMs requires specialized techniques available in the consortium. The team proposes an integrated collaboration building on the expertise and facilities of the different groups and capitalizing on the group’s access to OA patient materials. The project will run over three years.
(2) 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 group is pursuing a paradigm that an understanding of “in vivo intrinsic MSC” biology can be used to develop novel cost effective OA therapy strategies. The project aims to unravel the still unknown mechanisms that lead to cartilage repair (as observed in response to joint distraction) 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. The project will run over three years.

Testing another research funding approach, FOREUM awarded two research teams with pump prime funding designated to support their developing applications to the EU Horizon 2020 research programme.

(3) Dr. Ingrid Meulenbelt et al, Netherlands: Micro RNAs as biomarkers in OA

(4) Prof. Philip Conaghan et al, United Kingdom: OsteoArthritis definition through imaging and tissue biomarkers (PEARL-OA)
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. Major consideration was given to the theme of the call and to the wider needs of the community in the area of SLE research.

Research grants were awarded to the following teams who have started their research in between 2015 and early 2016.


Conventional and high-throughput approaches have revealed the involvement of several types of cells in lupus including lymphocytes, monocytes, neutrophils and endothelial cells, all of which originate from hematopoietic stem cells. Genetic association studies have identified a long list of loci associated with SLE but with limited evidence of functional (RNA-seq) provide a robust, unbiased approach for studying complex diseases and may expedite the functional annotations of these risk alleles and the discovery of novel biomarkers/targets of therapy. The applicants have completed a comparative transcriptome profiling by RNA-seq in the peripheral blood and kidneys of healthy individuals and SLE patients, and in the NZB/NZW murine model of SLE. They will examine the potential use of the discovered gene transcripts as biomarkers of disease activity, severity, morbidity, mortality and response to therapy in a large patient cohort and validate them in other European cohorts. To trace the fundamental immune aberrations in SLE (genetic or epigenetic) and uncover additional clues for disease pathogenesis, biomarkers for the disease and novel therapeutic targets, the team will extend their RNA-seq studies to hematopoietic stem cells derived from both murine and human lupus samples.

(6) Prof. Frédéric A. Houssiaux et al, Belgium: 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 systemic lupus erythematosus, impacting long-term survival and quality of life. Despite significant improvement in immunosuppressive drugs and regimens, at least 20% of LN patients do not achieve a sufficient level of response after 6 months of treatment, i.e. still display a significant amount of proteinuria. Since several studies have demonstrated that an absence of early response to therapy is a poor long-term renal prognostic factor, special care should be given to these patients. In order to test the efficacy of rituximab (RTX) in this niche indication, an investigator-initiated trial, entitled RING, was designed. LN patients with persistent proteinuria despite at least 6 months of standard of care (SOC) will be randomized in 2 groups. Half of the patients will receive RTX (5g in 18 months) while the other half will continue SOC (with escape mechanisms in case of worsening). Renal remission rates at 24 months will be compared.

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. Study of paired repeat renal biopsy samples, after RTX or SOC, should allow the team to unmask the mechanisms of action of RTX.

(7) Dr. Y.K. Onno Teng et al, Netherlands: 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, Sweden: 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 SpA 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.
(9) Dr. Uta Syrbe et al, Germany: 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.

(10) Prof. Dominique L. P. Baeten et al, Netherlands: 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.

(11) Dr. Philip Gardiner et al, Ireland: 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).
Upcoming FOREUM calls for research proposals

Thanks to the good financial situation of FOREUM and the 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. One topic is ready for launch in January 2016, another has been approved for launch in the summer of 2016. 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.

The next calls for proposals have been set as follows:

- **A call for research proposals on Registers in January 2016.** 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 wishes to instigate research, which will increase the utility of such databases for the wider community. Added value may include, for example, assessment of safety across different modes of action, real world comparison with outcomes from randomised trials, and integration of data from different registers or countries to address questions difficult to study in individual registers.

- **A call for research proposals in the area of Preclinical phases in rheumatic and musculoskeletal diseases in the summer of 2016.**

At their last meeting, the Board of Trustees and the Executive Committee have reviewed the funding model for approved calls and individual projects. It is agreed that some flexibility should be applied with regard to the total amount allocated for a specific call, currently set at € 1,000,000. In specific cases, FOREUM may also consider granting a higher amount per project than the currently applied ceiling of € 300,000 for successful individual projects. With this flexibility the Board can better accommodate the needs of multi-centre research teams and also pursue its goal of fostering rheumatological research of the highest quality.
FOREUM as an independent foundation is currently still in a build-up state in organizational terms. In 2015, the foundation established a 40-percent administrative position at its secretariat dedicated to supporting the FOREUM committees in their work, managing the research grant agreements with PIs, 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 also 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 2015, administrative expenses accounted for approx. 3.5 percent of the overall donation income.
In 2015 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:

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