# European League Against Rheumatism (EULAR)

*Position Paper*

## Horizon 2020 Framework Programme

*EULAR's position and recommendations*

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# Horizon 2020 Framework Programme
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**EXECUTIVE SUMMARY**

Rheumatic and musculoskeletal diseases (RMDs) comprise all painful conditions of the musculoskeletal system. More than 200 different diseases have been identified, which affect the joints, tendons, ligaments, bones and muscles, while some of these disorders also involve internal organs. Common symptoms are pain, swelling, and stiffness, common consequences are loss of locomotor function and premature death. Many of the RMDs, such as arthritis and osteoporosis are among the most common diseases in Europe.

**As part of its contribution to the debate on the future thematic domains for the next research framework programme and in order to make decision-makers and the public aware of the importance of supporting research on musculoskeletal diseases (RMDs) in Europe, the European League Against Rheumatism wants to state that:**

- **People from all age groups and both genders can develop a rheumatic and musculoskeletal disorder**. They affect the largest number of individuals in the industrialised world with up to **one third of people of all ages** being affected at some point during their lifetime. The consequences for the people concerned include impaired quality of life, reduction of physical function, disability and often premature death.

- **Musculoskeletal pain is experienced by most people at some time**. Only 15% of 20-72 year-olds reported no pain during the previous year, whereas 58% reported musculoskeletal pain during the previous week and 15% had musculoskeletal pain every day during the last year.

- **In Europe, chronic RMDs affect around one-quarter of the population (more than 120 million)**. The burden of some of these conditions is increasing with ageing as well as with changes in lifestyle risk factors, such as obesity and reduced physical activity. Other disorders can occur at any age, such as in children or in young and middle aged women and men.

- **In Europe, rheumatic and musculoskeletal conditions represent an economic burden of estimated 240 billion Euros per year**, with growing tendency due to demographic development and behavioural changes. The direct cost of RMDs within the EU is estimated to be 2% of its GDP.

- **RMDs elicit the highest costs to European health care and socioeconomic systems**, by virtue of direct expenses for medicines, surgery, physiotherapy, hospitalisation and rehabilitative measures but also indirectly by production losses, sick leave and disability pensions.

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- **Rheumatic and musculoskeletal diseases represent the main cause of disability and premature retirement among workers since they cause more functional limitations in adults than any other group of disorders**. 72.9% of workers report exposure to risk factors of RMDs during their working life. In 2005 RMDs accounted for the loss of 6.5 million workdays with an overall cost of 650 million Euros.

- The prevalence of RMDs will increase dramatically in conjunction with the ageing of the European population

**Given the great number of Europeans affected by RMDs and the burden these diseases pose on individuals in terms of mobility, working capacity and quality of life and given the severe consequences these diseases present on European health care systems and societies in terms of productivity loss and health care costs, EULAR is convinced that**

- Basic research and translational research in RMDs should be prioritised on the EU and Member States health research agendas at least in the same way as other major diseases. Medical research priorities should be defined in terms of societal challenges and the burden on both individuals and society; the traditional focus on mortality as the sole criterion for prioritisation is an outdated concept, unable to address the problems of the future.

- The Member States should, in collaboration with the EU, develop a consistent research strategy which takes into account the development of better therapies and treatments for RMD patients as well as approaches to personalized care. This will certainly need more funding as well as better coordinated and more integrated research activities at European level. The research strategy should be coordinated with other EU strategies in the field of health to create synergies.

- Research in RMDs should be targeted to improve early diagnosis, prevention and treatment of these diseases. These research areas are crucial since they help to significantly decrease the burden of RMDs for individuals and society.

- A coherent European strategy for the treatment and prevention of musculoskeletal diseases can only be developed when accurate and comprehensive data on these diseases and their risk factors are collected.

- In situations of scarcity of resources, research and innovation on different diseases should be funded in proportion to their burden.

**Considering the fact that the burden of RMDs is dramatically increasing due to an ageing population and different lifestyle factors it is about time that research in these conditions becomes a priority in the next framework programme.**

# Horizon 2020 Framework Programme
## *EULAR's position and recommendations*

### Introduction

With this paper, the European League Against Rheumatism (EULAR) is pleased to contribute to the debate on the development of the new Research Framework Programme, which is expected to be implemented once the current FP7 comes to an end in 2013.

The ideas and recommendations included in this document do not only aim at broadening the scope of solutions for people with rheumatic and musculoskeletal disease. These ideas and recommendation also intend to contribute to the debate on the future Research Framework Programme. In this sense, they have been developed with a view to the Europe 2020 strategy and the overarching aims of the Innovation Union.

This document was written with the collaboration of the rheumatic and musculoskeletal diseases community in Europe: scientists, health professionals and people with RMDs.

### About EULAR

The European League Against Rheumatism (EULAR) is the European umbrella organisation which represents scientific societies, health professionals associations and organisations of people with arthritis/rheumatism throughout Europe.

With 45 scientific member societies, 36 patient organisations coming together under the roof of the Standing Committee of PARE (People with Arthritis/Rheumatism in Europe), several health professionals associations, and corporate members, EULAR underscores the importance of combating rheumatic diseases not only by medical means, but also through a wider context of care for rheumatic patients and a thorough understanding of their social and other needs.

The aims of EULAR are to reduce the burden of rheumatic diseases on the individual and society and to improve the treatment, prevention and rehabilitation of musculoskeletal diseases. To this end, EULAR fosters excellence in education and research in the field of rheumatology. It promotes the translation of research advances into daily care and fights for the recognition of the needs of people with rheumatic diseases.

EULAR supports research projects in rheumatology by funding collaborative research between European rheumatology groups in fields that are in line with the mission, goals and strategies of EULAR. It has also developed a programme of special awards to recognise special achievements in the field of rheumatic diseases.

As part of its commitment with excellence in research and innovation, EULAR strongly promotes the involvement of patients in scientific activities. As one of the key recommendations to EU institutions and Member States included in the Brussels Declaration (2010) EULAR stated that 'People with RMDs are the experts at living with their condition and should be involved in the design, delivery and evaluation of the services they use', and EULAR applies the same principle to research. To support this approach, EULAR has funded a Patient Partners Research programme to provide training and support to people with RMDs. This course empowers participants to maximise their effectiveness in

discussions with scientific colleagues when determining the scope, design and evaluation of research projects in the area of RMDs, thereby ensuring a patient- centred focus. "In order to enable the successful inclusion of the patient perspective in EULAR-funded scientific research projects, EULAR has developed the EULAR Recommendations for the inclusion of patient representatives in scientific projects in 2010." [1]

## The challenge of rheumatic and musculoskeletal diseases for European societies

Rheumatic and musculoskeletal diseases (RMDs) comprise all painful conditions of the musculoskeletal system. More than 200 different diseases have been identified, which affect the joints, tendons, ligaments, bones and muscles, while some of these disorders also involve internal organs. Common symptoms are pain, swelling, and stiffness, common consequences are loss of locomotor function and premature death. Many of the RMDs, such as arthritis and osteoporosis are among the most common diseases in the in Europe.

In the public health field, some diseases and conditions attract most of the attention from the public opinion, policy makers, as well as scientific institutions and research funding organisations. Cardiovascular diseases, cancer, etc. are usually high on the agendas as they are responsible for millions of deaths every year, around 70% of all disease-related deaths in Europe.[2]

The predominant focus on mortality rates as the main criterion for deciding what diseases are important might have driven public opinion, policy makers and research funding institutions to neglect other diseases that produce an enormous burden on individuals, families and societies. These other diseases are probably not as relevant as other chronic diseases in terms of the number of people they kill in a short term. But they are extremely relevant in terms of their effects on the productivity of our economies, the sustainability of our health and social security systems, and –last but not least– the quality of life of people and their relatives.

Rheumatic and musculoskeletal diseases are among this group of health issues that have been neglected for many years or at least have not received enough attention in spite of the extremely high number of people affected, the reduced life expectancy associated with many of the RMDs, and their economic and social consequences.

In Europe, more than 120 million people (one out of four citizens) suffer from a chronic musculoskeletal condition. Many of them have developed some sort of disability or impairment, which reduces their mobility, limits their independence and, in a large number of cases, prevents them from continuing normal working and social lives.

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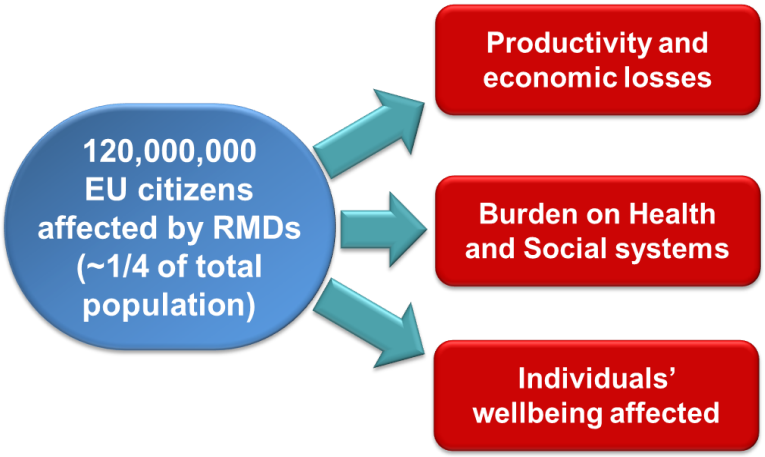
1 M P T de Wit et al (2010): *European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects*; Ann Rheum Dis doi:10.1136/ard.2010.135129

2 Data from 2005. WHO European Observatory on Health Systems and Policies (2010): **Tackling Chronic Diseases in Europe. Strategies, interventions and challenges**; Observatory Studies Series Nº 20, UK.




The number of people affected by RMDs as well as the disabling characteristics of these conditions have also a very negative impact on the European economy. Being the most common cause of severe long-term pain and physical disability, they represent the main cause of early retirement and long-term sick leave in Europe, which significantly affects the productivity and costs of companies across Europe.

Finally, the third pervasive consequence of rheumatic and musculoskeletal diseases is the enormous burden they put on health and social systems. To give an example, direct costs associated with the treatment and care of people with musculoskeletal conditions are of the order of 2% of the GDP every year.

The table below shows some data available regarding the impact of these disorders on individuals and societies.

| Burden | Evidence |
|---|---|
| **MORBIDITY:**<br><br>Rheumatic and Musculoskeletal Diseases are one of the **largest groups of diseases in Europe** | • Around **120.000.000 European citizens** (**25% of the total population**) are affected by some type of Rheumatic and Musculoskeletal Disease[3];<br>• **Up to ⅓ of European citizens of all ages** suffer from RMD at one point in their lifetime[4];<br>• A survey on musculoskeletal pain concluded that:<br>  ○ **85% of people** between 20 and 72 years suffered from musculoskeletal pain during the **previous year**<br>  ○ **15% of people** between 20 and 72 years suffered from musculoskeletal pain **every day** during the previous year<br>  ○ **58% of people** between 20 and 72 suffered from musculoskeletal pain during the **previous week**<br>• The **quality of life of approximately 7,5% of the European population** is severely and permanently reduced by pain and functional impairment caused by rheumatic diseases.[5] |
| **DISABILITY AND EMPLOYMENT:**<br><br>RMDs represent the **main cause of disability and premature retirement** among European workers[6] | • In 2005 RMDs constituted **39% of the total occupational diseases** recorded by the European Occupational Disease Statistics in 12 Member States[7]<br>• **In Sweden, up to 60% of persons** on early retirement or long-term sick leave claim musculoskeletal problems as the reason[8]<br>• **In France, 6.5 million workdays were lost** due to RMDs in 2005[9]<br>• **In Europe, 72,9% of workers report exposure to risk factors** of RMD during their working lives[10] |

[3] Estimation based on European Science Foundation (2006): **Rheumatic Diseases – a Major Challenge for European Research and Health Care**; European Science Foundation Policy Briefing, June.

[4] European Science Foundation (2006): **Rheumatic Diseases – a Major Challenge for European Research and Health Care**; European Science Foundation Policy Briefing, June.

[5] Ibid.

[6] EUMUSC.NET (2011); European Parliament, Written Declaration of the European Parliament on Rheumatic Diseases ((2009/C 285 E/11), http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:285E:0067:0068:EN:PDF .

[7] EUMUSC.NET (2011); European Occupational Disease Statistics 2005.

[8] Woolf A. & B Pfleger,(2003): **Burden of musculoskeletal conditions**, p. 8.

[9] European Agency for Safety and Health at Work (2010**): OSH in figures: Work-related musculoskeletal disorders in the EU – Facts and figures**, p. 100.

[10] European Agency for Safety and Health at Work (2010**): OSH in figures: Work-related musculoskeletal disorders in the EU – Facts and figures**, p. 100.

| Burden | Evidence |
|---|---|
| **COSTS:**<br><br>Rheumatic and Musculoskeletal Diseases represent one of the **highest costs to European health care and socioeconomic systems** | • RMDs are the second most common reason for consulting a doctor (10-20% of primary care consultations in most countries)[11]<br>• RMDs represent a **burden of 240 Billion Euros per year**<br>• The direct costs of RMDs in EU is estimated to be of **2% of the GDP**<br>• In Germany, the productivity loss due to musculoskeletal conditions was of **€ 23,9 billion** in 2006 **(~1,1% of GNP)**[12]<br>• Workdays' loss account for **650 Million Euros loss per year**. |

As it is possible to see from the data above, the burden of rheumatic and musculoskeletal diseases on individuals and societies is enormous, surpassing the impact of many of those diseases that usually get the attention of media and policy makers due to their higher mortality rates or their higher visibility.

But it is important to stress once more that rheumatic and musculoskeletal diseases represent the most disabling group of diseases affecting the working population, explaining most of the early retirement from the labour market. This not only imposes and enormous burden on the overall economy and on the health and social systems. It also affects the quality of life of dozens of millions of people throughout Europe, not only in terms of their mobility but also in terms of their economic wellbeing.[13]

No other disease affects such number of people, compels such number of workers and employees to leave the labour market either temporarily or permanently, and represents a comparable cost for the overall economy as well as for the health and social systems. Moreover, the burden is going to be much more important in the future if EU Member States do not properly address them, as the ageing of the population will mean that more and more people will be at risk of developing such disorders.

As the European Parliament acknowledged in Written Declarations in 2005 and 2008, and as representatives from EU institutions and Members States recognised at both the EU Presidency Conference on Rheumatic and Musculoskeletal Diseases and at a EU Ministerial Conference held in October 2010, research, innovation and development in this area are crucial. Only by having a better understanding of these diseases, it will be possible to innovate in the prevention and treatment of these diseases and thereby, reduce their burden on individuals, their families and societies as a whole.

[11] Woolf A. & B Pfleger,(2003): **Burden of major musculoskeletal conditions**, in Bulletin of the World Health Organisation, p. 653.

[12] EUMUSC.NET 2011; SUGA 2006.

[13] Disable people are significantly more likely to be poor than not disable people (European Disability Strategy, 2010).

## Most common types of rheumatic and musculoskeletal diseases. Characteristics and trends[14]

The impact of musculoskeletal disorders on individuals and society is expected to increase dramatically. Many of these conditions are more prevalent or have a greater impact in older patients, and the predicted ageing of the European population will markedly increase the number of people affected by these conditions. In addition, changes in lifestyle factors, such as increased obesity and lack of physical activity will further increase the burden.

*Osteoarthritis*

Osteoarthritis is characterised by focal areas of loss of articular cartilage within synovial joints, which are associated with hypertrophy of bone (osteophytes and subchondral bone sclerosis) and thickening of the capsule. The condition results in joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation. It can occur in any joint but is most common in the hip, knee and the joints of the hand, foot, and spine. Worldwide estimates are that 9.6% of men and 18% of women aged above 60 years have symptomatic osteoarthritis. Importantly, only little advance regarding pathogenetic insights and especially pharmacological therapies aiming at treating established disease or preventing its occurrence has been made in this area over the last decade.

*Rheumatoid arthritis*

Rheumatoid arthritis is an inflammatory condition with widespread synovial joint involvement. It is the most common form of inflammatory arthritis in Europe. Although it is a systemic disease, it predominantly affects peripheral joints. It affects 0.3 – 1.0 % of the general population and is more prevalent among women.

*Osteoporosis*

Osteoporosis is characterised by a low bone mass and a microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. It is recognised by the occurrence of characteristic fractures after low-energy trauma, the best documented of theses being fractures of the hip, vertebrae, and distal forearm. Hip fracture is the most detrimental fracture, being associated with 20% mortality and 50% permanent loss in function. The number of osteoporotic fractures is predicted to increase across Europe due to the ageing population.

*Low back pain*

Low back pain is a major health and socioeconomic problem in European countries. It usually is defined as pain localised below the line of the twelfth rib and above the inferior gluteal folds, with or without leg pain. Low back pain can be classified as “specific” (suspected pathological cause) or “non-specific” (about 90% of cases). It affects over 80% of people at some point during their life. Most episodes of pain settle after a couple of weeks but many have a recurrent course. Frequently low back pain never fully resolves, and patients experience exacerbations of chronic low back pain.

[14] This section is based on Anthony D Woolf & Bruce Pfleger “Burden of major musculoskeletal conditions”, Bulletin of the World Health Organisation 81(9), 2003.

*Ankylosing spondylitis*

Ankylosing spondylitis is a form of chronic inflammation of the spine and the sacroiliac joints. Chronic inflammation in these areas causes pain and stiffness in and around the spine. Over time, chronic inflammation of the spine (spondylitis) can lead to a complete cementing together (fusion) of the vertebrae, a process referred to as ankylosis. Ankylosis leads to loss of mobility of the spine.

*Psoriatic arthritis*

Psoriatic arthritis occurs in people with Psoriasis, a common skin disease; psoriatic arthritis affects the joints by virtue of a painful and destructive inflammation, but also elicits inflammation of the spine and painful tendon insertions, frequently leading to severe disability

*Gout*

Gout is a painful type of arthritis that causes sudden, severe attacks of pain, tenderness, redness, warmth, and swelling in the joints, especially the big toe. The pain and swelling associated with gout are caused by uric acid crystals that precipitate out of the blood and are deposited in the joint.

*Fibromyalgia*

Fibromyalgia syndrome is a chronic condition characterised by body aches, widespread pain, sleep problems, extreme fatigue, depression, anxiety, and other symptoms, in combination with tenderness of specific areas (muscles and tender points) of the body.

*Connective Tissue Diseases*

Connective tissue diseases including Systemic Lupus Erythematosus and Scleroderma cause chronic inflammation and loss of function of skin, joints and internal organs. Although they are less common than of most of the other rheumatic diseases they have a higher morbidity, and the work and healthcare costs are greater. The understanding of the mechanisms responsible for the tissue damage and heterogeneity of these conditions is still very preliminary and at least a decade behind compared to inflammatory arthritis. Historically there have been few specific therapies aimed to modify the course of CTDs but there are several potential new approaches that .

## Contribution of research and innovation on rheumatic and musculoskeletal diseases to the European Union strategy and policies

The European Union has clearly defined the orientation of the EU research and innovation policy, aligning it to the overall objectives of Europe 2020 strategy. This strategy particularly aims at fostering a “smart”, “sustainable” and “inclusive” economy. It focuses on improving the productivity and sustainability of the European economies and societies, particularly through investment in innovation, an increase of employment rates, the improvement of the education of the population, the use of green resources and energies, and the social and economic inclusion of all citizens.

In the health and social sectors, the Commission has announced that research and innovation efforts will be defined in terms of their contribution to tackling specific societal challenges, such as the

consequences of ageing of the population or poor living conditions of a considerable proportion of the population.

Placing societal challenges (particularly the improvement of lifelong health, the increase of the number of working years, and the increase of reduction of dependency), at the core of the research and innovation policy in this area, implies that priorities should be given to those diseases and group of diseases representing a major barrier.

Having a healthy, active workforce is crucial for the achievement of the objectives established by the European Union for the next decade. Chronic diseases, particularly those preventing participation of individuals in the labour market, constitute one of the main barriers for increasing the productivity and competitiveness of our economies. In this sense, rheumatic and musculoskeletal diseases represent a major societal challenge. Being the second cause of short-term sick leave (after respiratory diseases), one of the main causes of long-term sick leave, work disability and early retirement, rheumatic and musculoskeletal diseases represent a serious threat to health of our economies and social systems.

The prevalence of these types of disorders among certain groups of the population (ie the elderly), would counterbalance one of the key objectives of the Europe 2020 strategy: the increase of the participation of the population in the labour market, in particular of older people. Being as low as 46%, work participation of people aged between 55 and 64 needs to be increased significantly. Nonetheless, this population is the most affected by a number of chronic diseases, particularly by musculoskeletal conditions, that would to some extent prevent them from remaining in or returning to the labour market.

Improving the knowledge of the causes and mechanisms of these diseases is crucial for developing innovative therapies, treatments and medicines for improving the physical conditions of millions of people throughout Europe, and therefore for improving their employability.

Over the last years, research and innovation in rheumatic and musculoskeletal diseases has produced significant results that have positively impacted on the wellbeing of people with these disorders, reducing pain and improving their mobility among other results. Nonetheless, further investments are needed to produce a more significant impact. Although diagnosis and treatment of musculoskeletal conditions have improved in recent years, much more investigation is needed on the causes and mechanisms affecting the development of these disorders, while more investments are needed for producing innovative treatments.

The Innovation Union, and particularly the European Innovation Partnership on Active and Healthy Ageing, represent a good opportunity for addressing these issues from a comprehensive and integrated perspective.

As one of the key instruments of the Europe 2020 strategy, the Innovation Union proposes to focus on innovation in products, services and business models as a driving force. The overall idea is not only to increase the budget for research and innovation, but also to avoid fragmentation and duplication of resources and the lack of appropriate framework conditions for research and innovation.

In the context of the Innovation Union, research and innovation on rheumatic and musculoskeletal diseases will be very relevant for the implementation of the pilot Partnership on Active and Healthy Ageing. In general terms, this partnership aims at increasing the average healthy lifespan in the EU by bringing together all relevant actors in the demand and supply sides, by improving the framework conditions for innovation and research, by seeking to leverage financing and investments in innovation, and by improving coordination and coherence between funding for research and innovation at European, national and regional level in Europe.

Moreover, innovative research, as it is done in the major European scientific institutions focussing on RMDs, leads and will lead to new discoveries. Indeed, the principle of using biological agents for RMDs has developed in Europe. Expansion of these activities by respective support from the EU will lead to valorisation of these efforts. The market for biological agents and chemicals targeting important intracellular molecules is currently huge and further increasing, and there is a great opportunity for the European knowledge economy to be more successful in this respect in the future.

Thus, furthering research and innovation in rheumatic and musculoskeletal diseases is crucial for addressing some of the key societal challenges identified by the European Union, particularly regarding the increase of employment rates and the increase of the average healthy lifespan. In other words, the results obtained from research and innovation in this field would contribute to eliminate some of the most common physical barriers that prevent people to stay or return to the labour market and that prevent the elderly to have an active life.

## Rationale for topic proposals

Over the last years, European rheumatology research has contributed significantly to our current understanding of these diseases and to important therapeutic advances. Europe has been at the forefront of investigating pathways to disease, understanding their epidemiology, improving diagnostic and biometric approaches, and developing effective therapies against rheumatic diseases. Europe pioneered treatment with biological agents, such as blockade of tumour necrosis factor alpha (TNF-α), and additional new therapies targeting the molecules involved in the pathogenesis of chronic inflammatory disease have also been developed in recent years. In addition, basic research activities in molecular and cell biology as well as epidemiologic and clinical research have progressed and reflect further European strengths that influence global developments. However, these advances have been primarily exploited by non-European pharmaceutical industry.

At the current stage, the majority of rheumatic diseases can be treated symptomatically but **they cannot be cured yet because of insufficient information on causes and early pathogenic events. Future research should therefore also focus on prevention of rheumatic diseases and repair of damage.** Moreover, the events leading to tissue destruction are still insufficiently known with regard to when in disease progression particular cellular and molecular entities come into play or are affected. Likewise, the effects of tissue destruction on the innate and adaptive immune response are unknown. Understanding these events will open the arena for new diagnostic as well as therapeutic means.

Although the integration of basic, translational and clinical research as well as epidemiology has been developed to various degrees at the national level, integrated research at the European level is

lagging behind. Similarly, the efforts of the rheumatology sector in adult and paediatric rheumatology as regards translational research, epidemiologic research focusing on the complex aetiology and the burden of illness, as well as evaluative health care research, are mainly done at the national level.

Early diagnosis of RMDs is pivotal to allow for institution of effective therapies aiming at prevention of disability. Consequently, means to diagnose RMDs at the earliest time points or even allowing to diagnose evolving disease should be a major focus point for research activities of the coming years.

As elaborated few years ago by leading experts in rheumatic diseases commissioned by the European Science Foundation[15] research strategies on rheumatic diseases in Europe should in the coming years focus on:

- *Integration of successful national research efforts into a pan-European research strategy,*
- *Integration of basic, clinical and health care research for a fast translation of new concepts, and*
- *Integration of competence in developmental and molecular biology, genetics, immunology and systems biology.*

In this sense, integrated research efforts should focus on:

- *Better understanding of the molecular and cellular basis of chronicity in rheumatic diseases for the development of curative and preventive strategies;*
- *Better understanding of the pathways leading to severe comorbid conditions and premature mortality in the course of RMDs, such as lymphoma and cardiovascular disorders;*
- *Evaluating the incidence and outcome of rheumatic diseases and the development of prevention strategies and also to evaluate different therapeutic strategies for adults and children;*
- *Developing basic strategies for cell therapies of rheumatic diseases, especially immune ablation of pathogenic cells, reinstallation of tolerance and regeneration of degenerated or inflamed tissues.*
- *Better understanding of the molecular and cellular pathology of osteoarthritis and osteoporosis.*
- *Accurate phenotyping of the connective tissue disease patients and Identification of imaging and serological biomarkers of disease activity to better define clinical response in Connective Tissue Diseases.*

**Future priorities in research** should seek to achieve better **understanding of the initiation and pathogenesis of rheumatic diseases**, their common and disease-specific principles. This understanding should develop into strategies to prevent the development and aggravation of rheumatic diseases by targeting these events.

Specific research for the future should comprise research on the **mechanisms leading to degenerative joint disease, such as osteoarthritis of the hands and the large joints**, aiming at

[15] See ESF Policy Briefing "**Rheumatic Diseases – a Major Challenge for European Research and Health Care**", June 2006. Accessible at: http://www.esf.org/publication/223/spb26RheumaticDiseasesfinal.pdf

preventing their occurrence and on innovative therapies that include targeting molecules involved in changes of cartilage and bone and fostering cell and matrix regeneration. The same is true for interdisciplinary research on the **mechanisms of inflammatory bone and joint destruction,** aiming at the development of targeted combination therapies as well as regenerative therapeutic strategies.

Furthermore, strategies to develop **vaccines for adults and children with autoimmune rheumatic diseases** will generate innovative knowledge on immunodeficiency of autoimmune patients and translational information on benefits and risks of vaccination. Combinatorial research on the **connectivity of chronic inflammation with autoimmunity as well as degenerative changes of cells and matrix** will be of utmost relevance to the European population and requires a pan-European research effort, because of the dispersed competence and necessity of interdisciplinary interaction.

The latter in particular would also be an overdue European contribution to the WHO **Bone and Joint Decade (2000-2010).** By fostering interdisciplinary research on those topics, the EC would contribute to the WHO goals: increase in quality of life of patients with rheumatic diseases, reduction of socioeconomic burden, **development of prognostic diagnosis and curative therapies and prevention strategies.** There is a strong necessity for more instruments in the area of pan-European **epidemiologic research and innovative biometric approaches** focusing on early determination of efficacy or inefficacy of therapies in patient groups and individual patients, pharmacovigilance, safety, costs and socio-economic impact of new cost intensive therapies. This can only be achieved in industry independent approaches, pan-European networking and study registries. Pan-European networks are also required for **joint clinical trials of novel therapies** with sufficient patient numbers.

**Rheumatic diseases are a paradigm for breakdown of tissue homeostasis, autoimmunity and chronic inflammation**, and results and innovations in therapeutic concepts will have a high translational potential for most rheumatic diseases as well as other diseases with immunological and nonimmunological pathogenesis, e.g. infection, allergy, cancer, atherosclerosis etc. **The research on rheumatic diseases and autoimmunity would strengthen European expertise in health care with enormous economic and social impact for Europe.** They would shape research by creating networks combining research areas with little interaction so far, thus generating a competitive advantage for Europe in the respective emerging research fields and the chance to develop innovative products and therapies with high translational potential for all diseases with inflammatory and non-inflammatory components.

**Proposals for research topics for the new Research Framework Programme**

| **Topic:** | **Identification of pathological pathways in chronic joint inflammation in man: Understanding the mechanisms leading to rheumatoid arthritis and seronegative arthropathies including ankylosing spondylitis** |
|---|---|
| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Chronic inflammation leads to significant morbidity, disability and mortality. Although similar molecules may be involved in the ultimate disease pathways, the genetics of rheumatoid arthritis and seronegative spondylarthropathies are clearly different as are other immunological phenomena. In order to understand the different pathomechanisms, there is need for European coordination of prospective cohorts of patients who are clinically well characterized and evaluation of the role of infectious antigens, T-cell reactivates, antigen presentation, innate immunity, proinflammatory cytokines, genomics and proteomics as well as association with clinical outcome to be assessed by reliable tools. |
| **Impact:** | These data will provide an opportunity for identifying factors that cause disease, and also to establish novel therapeutic targets or even prevention of the diseases. |
| **Funding:** | 2 projects should be funded – the one focused on RA, the second on seronegative arthritis, Community funding - 12€ Mill. |

| **Topic:** | **Identification of pathological pathways in chronic joint inflammation: translation of human disease mechanisms into relevant animal models and in vitro test systems for preclinical testing of novel therapeutic strategies (from bedside to bench)** |
|---|---|
| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | This research action aims at the direct analysis of chronic inflammation in human (rheumatic) disease, ex vivo and in vitro, using genomic, proteomic and cytomic technologies, to define cells (haematopoetic and/or mesenchymal), relevant proteins, genes and pathways, and to translate this information into the development of new, relevant animal models and in vitro systems of chronicity in inflammation, for the validation of molecular concepts of chronic inflammation and an improved preclinical testing of novel therapeutic strategies and targets. |
| **Impact:** | |
| **Funding:** | Two projects should be funded – each with 5 Mill Euro. |

| Topic: | **Studying pathomechanisms (Cytokines, dendritic cells, regulatory T-cells, autoreactive T cells, B cell subpopulations) involved in autoimmunity as possible future targets of therapeutic approaches in connective tissue diseases** |
|---|---|
| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Connective tissue diseases (CTD) represent a group of inflammatory rheumatic autoimmune diseases including systemic lupus erythematosus (SLE), primary Sjögren's syndrome (SS), systemic sclerosis (SSc), autoimmune myositis and overlap syndromes such as mixed connective tissue disease (MCTD, Sharp syndrome). They mainly occur in young and middle-aged women. They have in common the occurrence of autoimmunity, but the manifestations of the diseases differ as does their therapy. Currently, there is no curative treatment for most patients with these diseases. Current treatment includes chronic administration of steroids and immunosuppressive drugs. |
| **Impact:** | By focusing research on the underlying immunopathology, novel and curative therapies should be developed. |
| **Funding:** | Commission funding – 10 Mill Euro (two projects). |

| Topic: | **Identification of imaging and soluble markers predictive or prognosis and to measure disease activity and clinical response in patients with Connective Tissue diseases** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Connective tissue diseases (CTD) represent a group of inflammatory rheumatic autoimmune diseases including systemic lupus erythematosus (SLE), primary Sjögren's syndrome (SS), systemic sclerosis (SSc), autoimmune myositis and overlap syndromes such as mixed connective tissue disease (MCTD, Sharp syndrome). No definite disease modifying drugs have been identified for CTDs. The design and conduct of intervention trials in these conditions is hampered by the lack of accurate disease phenotyping and poor outcome measures to determine clinical response |
| **Impact:** | The identification and validation of biomarkers will allow accurate design and assessment of efficacy of intervention trials and improve clinical management |
| **Funding:** | Commission funding – 10 Mill Euro (two projects). |

| Topic: | **Bioengineering approaches to tissue regeneration (with special emphasis on cartilage repair)** |
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| **Activity:** | **Biotechnology, generic tools and technologies for human health**<br>• *Innovative therapeutic approaches and interventions* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Recently progress has been made in treating inflammatory conditions such as rheumatoid arthritis (RA) with biological agents (anti-TNF and others). However this improvement in symptomatology has not been matched by a similar effect on cartilage regeneration. In conditions such as osteoarthritis (OA), significant damage to cartilage and other structures represents a major healthcare problem. Developing optimal techniques to generate cartilageneous tissue from various mesenchymal stem cell sources will be needed to advance this promising area of research into cartilage replacement and regeneration. This may allow reducing the need for prosthetic joint surgery. Understanding the detailed molecular mechanisms involved in repair enhance these efforts. Pan-European collaboration will be important to achieve these goals. This not only includes cooperation on cellular and molecular techniques, but also translation into clinical trials of larger scale than done to date. Collaboration with SMEs and regulatory authorities will be valuable. |

| Topic: | **Understanding immunosenescence (i.e. responsiveness of the immune system in late life) with the focus on autoimmunity, vaccination and infection** |
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| **Activity:** | **Translating research for human health**<br>• *Research on the brain and related diseases, human development and ageing* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Major changes occur in the immune system by the age of 60years. These changes affect both the innate and adaptive arms of the immune system and are associated with a hyperinflammatory state referred to as “inflamm-ageing”. It is not clear yet whether these changes are “natural” or caused by pre-existing conditions, but they are definitely associated with a reduced ability of the immune system to perform immune surveillance. Multidisciplinary approaches should elucidate the ageing process of the immune system with regard to early and late autoimmune diseases, immune responses to vaccines and infectious agents in elderly. Epidemiological, postgenomics, cell biology and immune monitoring should be integrated. Strategies for infectious disease prevention and health care in autoimmune patients and non-responders should be developed with perspective to public health. Strong involvement of biotechnological SMEs and public health authorities should be fulfilled. |

| Topic: | **Understanding of the molecular and cellular pathology of osteoarthritis and translation into clinical innovation** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Emphasis should be given to the basic understanding of degenerative rheumatic diseases, in particular osteoarthritis of the small and large joints, with the focus on underlying pathological processes and environmental factors, to stop the degeneration and initiate regeneration of the damaged tissue This project would integrate genomics, molecular and cellular approaches for the basic understanding of the contribution of inflammatory and anti-inflammatory components of the disease. Databases and biobanks of patients (and their controls) should be established together with well-coordinated methods for longitudinal surveillance of these patients concerning clinical features and biomarkers. Biological marker development, imaging technologies and regenerative approaches should result from this project. Strategies should be developed for effective transfer from the bench to bedside. |

| Topic: | **Understanding the mechanisms causing autoimmunity prior to development of RA and feasibility of treatment** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Autoimmune reactions develop many years before the onset of RA, and have, together with genotyping, predictive value for whether disease will develop in individuals who are seemingly healthy. These data provide a possibility for identification of factors that cause disease, and also to treat or prevent the disease before its actual clinical signs are visible. Research should include the role of autoantigens as well as proinflammatory cytokines. In order to explore this possibility for prevention of RA, there is a need for European coordination of prospective cohorts of patients at high and low risk for RA with prolonged follow-up, and for detailed immunologic studies of these individuals. |

| Topic: | **Understanding the mechanisms leading to joint destruction and means to enhancing repair in RA** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Use of novel therapeutic strategies in combination with imaging methods and molecular studies of mechanisms of joint destruction has already permitted a drastic reduction of destruction of cartilage and bone in RA. A further understanding of the detailed molecular mechanisms that cause the destruction and simultaneous studies on repair mechanisms may make it possible to combine therapies which stop destruction with therapies that enhance repair. In order to address these questions, there is a need for a European effort combining molecular studies on joint destruction and joint repair, with imaging techniques that can be used to diagnose and follow destruction as well a repair processes. |

| Topic: | **Development of molecular diagnostics (biomarkers) for rheumatic diseases including prediction of different disease courses and response to therapy** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Establishment and validation of novel biomarkers for early diagnosis of rheumatic diseases, such as osteoarthritis, rheumatoid arthritis, and seronegative (spondyl) arthritides, for monitoring of disease progression and efficacy of therapeutic approaches. Innovative technologies such as proteomics should be employed in clinically well-defined patient (sub)populations in long-term follow-up; clinical databases and biobanks will be invaluable in this respect. Industry should be involved for transfer into clinical application. |

| Topic: | **Developing effective vaccination strategies for children with rheumatic diseases** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Multi-disciplinary research of paediatric rheumatologists, immunologists and epidemiologists. Children with chronic inflammatory diseases are severely immuno-imbalanced and/or under continuous immunosuppressive therapy and there is no evidence on the safety and efficacy of different vaccines in children with rheumatic diseases. The aim should be to circumvent these obstacles and to provide these children with protective immunity against major and harmful infections. Multicentre studies should achieve the critical number of patients and provide evidence for efficacy and safety of vaccination strategies in paediatric rheumatology and providing harmonized and effective guidelines for clinical practice regarding immunisation in children with chronic inflammatory diseases. |

| Topic: | **Development of molecular diagnostics for autoimmune diseases and advanced immunotherapy** |
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| **Activity:** | **Translating research for human health**<br>• *Translational research in other major diseases (e.g. rheumatic diseases)* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Establishment and validation of novel marker systems and technologies for early diagnosis, monitoring of diseases progression and efficacy of biologics therapies as well as novel immunotherapies. Innovative technologies such as automated flow immunofluorescence should be combined with postgenomic data such as cell-specific gene signatures in multiparameter analysis for high specificity. Biotechnology industry should be involved for transfer into clinical application. |

| Topic: | **European studies and trials in order to evaluate the incidence and outcome of rheumatic diseases and the development of prevention strategies - Evaluation of different therapeutic strategies for adults and children with rheumatic diseases, including health economy aspects and research on the relevance of non-genetic risk factors (e.g. smoking, obesity, social status).** |
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| **Activity:** | **Optimizing the delivery of health care to European citizens**<br>• *Translating clinical research into clinical practice* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | Large, independent European clinical trials as well as coordinated pan-European research in epidemiology should aim to answer urgent questions pertaining to prevention and control of the diseases. Independent evaluation of therapeutic efficacy and its impact on the quality of health care and the health economy should be the result of this research network. |

| Topic: | **European network of paediatric rheumatologists and epidemiologists** |
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| **Activity:** | **Optimizing the delivery of health care to European citizens**<br>• *Translating clinical research into clinical practice* |
| **Projects type:** | Collaborative research projects |
| **Aim and focus:** | A Network of Excellence would serve for implementation of inception cohorts of particular juvenile rheumatic diseases and drug registries on new biologic therapeutic agents in paediatric rheumatologic clinical practice. These data are essential for tackling the most important issues in contemporary medicine, and will improve the limited knowledge on long-term outcome, predictors, life-time incremental costs of juvenile rheumatic diseases, as well as on the safety and efficacy of potent and expensive drugs in paediatric rheumatology. |