AMERICAN COLLEGE OF RHEUMATOLOGY
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Specialists in Arthritis Care & Research

1800 Century Place, Suite 250 • Atlanta, Georgia 30345-4300
Phone: (404) 633-3777 • Fax: (404) 633-1870 • www.rheumatology.org

American College of Rheumatology

# Research Agenda

*Approved by the ACR Board of Directors – November 2005*

## I. Executive Summary

Rheumatologic conditions are a major burden to the health of the U.S. population, causing substantial disability and taxing the limited resources of our health care system. People with these conditions receive much of their care from rheumatologists and allied health care professionals. These health care workers are represented by the American College of Rheumatology (ACR), including its division the Association of Rheumatology Health Professionals (ARHP). The ACR is an organization of professionals who share a dedication to healing, preventing disability, and curing the more than 100 types of arthritis and related disabling and sometimes fatal disorders of the joints, muscles, and bones. ACR membership includes practicing physicians, research scientists, nurses, physical and occupational therapists, podiatrists, physician assistants, biomedical engineers, psychologists, and social workers. The ACR seeks to promote research through its affiliated Research and Education Foundation (REF).

A major goal of the ACR is to promote basic, clinical and health services research in arthritis and rheumatic and musculoskeletal diseases in order to improve the care and clinical outcome of patients with rheumatologic conditions. To this end, the ACR supports research and education through its annual meeting, the publication of its journal *Arthritis and Rheumatism*, the provision of a limited number of grants and awards, advocacy for increased funding of rheumatology research, and collaboration with its affiliated Research and Education Foundation (REF). The ACR Committee on Research (COR) is responsible for facilitating the research goals of the organization and provides leadership in research and research training in rheumatology and related professions. To this end, the COR established a Task Force to develop a research agenda which is subject to the approval of the ACR Board of Directors. This research agenda comprehensively addresses the important areas for research in rheumatic diseases and it targets the needs for new technology, infrastructure, and increased funding.

## II. Introduction

- **Burden of disease**

Rheumatologic conditions are a diverse group of disorders that often lead to pain, physical disability, reduced quality of life, co-morbidities, and increased mortality. They also affect the psychological status of individuals as well as adversely impact careers and families. Since many rheumatologic conditions pursue a chronic or relapsing course, their detrimental effects accumulate over time, leading to reduced quality of life, high rates of work and role disability, and substantial use of health care services.

Based on surveys carried out in the U.S., rheumatologic conditions produce physical disability in an estimated 4 – 5% of the population (1). In the U.S. alone, over 12 million people suffer from symptomatic osteoarthritis of the hands, while over 8 million people are affected with pain from osteoarthritis of the knees (2). Regional pain disorders such as low back and neck pain are particularly frequent complaints of the population where, in the U.S., more than 56 million people have reported symptoms of low back pain, and nearly 30 million people have had symptoms of neck pain (2).

Many diseases in rheumatology produce acute and chronic inflammation of joints and other tissues. Rheumatoid arthritis (RA), the most common cause of chronic inflammatory arthritis, has been estimated to affect nearly 1.2 million individuals in the United States. RA often culminates in joint damage and disability,

and is also associated with increased risk of cardiovascular disease and mortality. However, recent therapeutic advances have been shown to improve signs and symptoms, reduce radiographic joint damage, and lessen physical dysfunction over the short-term (e.g. a few years). The spondyloarthritides comprise ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated spondyloarthropathy and they exhibit a prevalence not much unlike that of RA. Gout, another cause of joint inflammation, affects about 4 million people in the United States (2). While many of these cases represent acute, self-limited attacks of arthritis, an estimated several hundred thousand patients suffer from either frequent recurrences of gout or chronic gouty arthropathy. The reported rates of occurrence for other conditions may be less precise, but they nevertheless underscore the high burden of rheumatologic disease. Polymyalgia rheumatica and giant cell arteritis, rheumatologic disorders which typically target older individuals, have been reported to occur in 676,000 and 217,000 persons, respectively. For many conditions in rheumatology, women are disproportionately affected more often than men. As an example, primary Sjögren's syndrome affects predominately women, with an occurrence rate nearly matching that of RA. In addition, systemic lupus erythematosus occurs in women much more than men (ratio of approximately 10:1). Among adult women in the U.S., the prevalence of physician-diagnosed systemic lupus erythematosus (SLE) has been estimated to be 100 per 100,000, which projects to 108,300 (3).

Rheumatologic diseases are much less common in children than adults. However, they are an important group of diseases because of their damaging affects on growth and development. The most common diagnostic category of childhood rheumatologic disorders is juvenile idiopathic arthritis (JIA), which encompasses several different conditions, including those previously classified as juvenile rheumatoid arthritis (JRA). A United States study found the prevalence of juvenile chronic arthritis (JRA) to be 86 per 100,000 children (4). Based on the 2000 census, this result would translate to approximately 60,000 children in the United States with JRA (4); estimates for the broader diagnostic category of JIA would be higher than the number of children with JRA. Other pediatric rheumatologic diseases occur with much less frequency, but they may nevertheless have devastating effects on the health of children.

Many rheumatologic conditions exert a major toll on people, families, and society due to their relatively high prevalence in the population. Moreover, many of these conditions are chronic, and lead to significant pain and disability over the long-term. Considering the aging and changing lifestyle (e.g. increased rates of obesity) of the population, rheumatologic diseases in general are likely to have an even greater impact in the future.

- **Goals**

The American College of Rheumatology is seeking to promote research in both adult and pediatric rheumatology, with the following aims:

- Identify important areas of research
- Stimulate promising research that will lead to improved heath outcomes
- Expand funding to boost the amount of research
- Increase access to new research methodologies and technologies
- Foster the development of patient registries, data sharing, tissue repositories, research consortia, and other shared resources to enhance research capabilities
- Cultivate interdisciplinary and inter-professional research to address complex problems that cut across traditional medical disciplines and health care professions
- Ensure an adequate supply of well-trained clinician-scientists

## III. Methodology

The Board of Directors of the American College of Rheumatology (ACR) charged its Committee on Research to develop a research agenda, hereafter termed the ACR Research Agenda. Dr. E. William St. Clair was appointed by the Committee Chair, Dr. Jane Salmon, to form a Task Force of external advisors to assist in drafting a document for this purpose. The members of this Task Force are listed below in Section V. The

members include representatives of both the ACR and the Association of Rheumatology Health Professionals, adult and pediatric rheumatologists, and the Committee on Rheumatologic Care. An initial draft of the ACR Research Agenda was created by the Task Force. This draft was subsequently discussed by teleconference and edited according to consensus of the members of the Task Force. The Task Force also obtained input from a forum which was sponsored by the ACR Research and Education Foundation and designed to identify key research initiatives in RA. The intent of the Task Force was to ensure as much as possible the alignment of these overlapping ACR activities. After approval by the Committee on Research, this document was then sent to the Executive Committee of the Board of Directors for feedback, which was followed by further editing of the document. An approved draft was posted on the ACR web-site for public comment, with subsequent modification and submission to the Board of Directors for final approval.

## IV. Research Priorities

- **Etiology of Disease**

There are different types of research that can be carried out in both adults and children that shed light on our understanding of arthritis and other rheumatologic diseases, as well as their assessment and treatment. Some research focuses on the etiology of disease. For example, many of these diseases develop in genetically-susceptible individuals. This genetic predisposition is evidenced by the aggregation of many rheumatologic diseases in families and the links found between specific diseases and the presence of certain genotypes (e.g. rheumatoid arthritis and certain genes of the major histocompatibility locus). The identification of genetic markers may define subsets of disease with varying prognosis, provide more insights into disease mechanisms, or predict treatment responses. Further investigation is needed to understand the opportunities and limitations of the genomic approach to disease.

While an individual's susceptibility to a particular disease may be influenced to some extent by their genetic make-up, it may also depend on environmental exposures, such as infection or toxic exposure. An example of a toxic exposure implicated in the pathogenesis of a rheumatologic disease is the epidemic of eosinophilia-myalgia syndrome that occurred in 1989 from the ingestion of L-tryptophan containing trace quantities of contaminants. Elucidating these associations as well as clarifying their interactions with genetic factors will contribute significantly to our knowledge about disease causation. Large, multidisciplinary epidemiological studies are a way to collect this type of information.

Examining the natural processes by which the immune system functions also may shed light on the causes of rheumatologic diseases in the category of autoimmunity. Autoimmune diseases occur when the immune system of an individual attacks the body's own tissues. The development of T or B cells with the capacity to recognize self-tissues is a normal process. However, these self-reactive immune cells may cause damage and produce autoimmune disease when they fail to become properly "tolerized" or silenced in the individual, either by elimination, inactivation, or regulation. Understanding the regulation of these processes in the normal and disease state is vital to elucidating the mechanisms involved in autoimmunity.

- **Mechanisms of Disease**

Much research has focused on the pathogenic mechanisms involving immunity and inflammation. In RA, for example, investigation of both animal models and patients with this disease has deepened considerably our understanding about the roles of the adaptive and innate immune systems in causing joint inflammation and damage. These studies have revealed new therapeutic targets, such as tumor necrosis factor and interleukin-1, leading to major advances in patient care. These findings have also translated into therapeutic breakthroughs for diseases such as ankylosing spondylitis and psoriatic arthritis.

Another example is the recent explosion in knowledge about the complement system. The complement system is vital for host defense, and its activation has been implicated in the pathogenesis of numerous rheumatologic diseases, including SLE. Recent studies suggest that monitoring of certain products of the

complement system may serve as tools for improving diagnosis, measuring disease activity, assessing prognosis, or determining response to therapy. Activation of complement has also been shown recently to play a key role in the recurrent miscarriages associated with the anti-phospholipid antibody syndrome. Emerging from this work has been the concept that the complement pathway could be a new therapeutic target for this disease. New insights have been similarly gained about the mechanisms involved in vasculitis, myositis, and systemic sclerosis, but much more is to be learned about the molecular details of these disease processes.

Osteoarthritis, a major cause of morbidity in the elderly, is characterized by loss of articular cartilage, formation of osteophytes, changes in the subchondral bone, and varying degrees of synovial inflammation. Several approaches may improve our knowledge of the causes of osteoarthritis. The investigation of abnormal biomechanics, cartilage metabolism, and changes in subchondral bone offer new opportunities to address the basis of disease progression. Understanding the pathways involved in normal bone structure and growth, as well as the systemic factors that can modify this process, will undoubtedly provide new ways to explore the pathogenesis of osteoarthritis. The discovery and validation of biochemical markers may help to identify those individuals with a higher likelihood of osteoarthritis progression. Imaging modalities with increased sensitivity to change in joint structure over time compared with standard radiographs may prove to be useful for precisely quantifying disease progression. Technology, including computerized gait analysis, may also serve as a means of objectively studying a patient's function in vivo and improving understanding of joint structure-function relationships.

- **Advances in Therapy**

Increased knowledge about the benefits and risks of treatment come from results of well-designed clinical trials. Initially, novel therapies may be tested in small studies designed to establish proof-of-principle often using biomarker or imaging endpoints. Promising interventions, such as drugs and behavioral therapies, can be evaluated in randomized, placebo-controlled trials to establish clinical efficacy and safety in a specific disease population. These trials typically plan for the study of hundreds or even thousands of participants from multiple centers to provide sufficient statistical power to detect an effect of the experimental treatment, if one exists.

Novel cell-based technologies such as tissue engineering and gene therapy provide avenues to enhance the normal repair process of joint tissues, such as cartilage and bone. Alternatively, cell-based approaches can be used to deliver biologically active factors to specific sites in the body that interdict factors involved in disease pathology. Despite rapid advances in these areas, significant challenges remain to successfully translate tissue engineering and gene therapy into viable treatment strategies. Solving this complex problem will require the cooperation of numerous disciplines in the fields of cell and molecular biology, bioengineering, biomaterials, orthopaedic surgery, and rheumatology.

Because of their collaborative nature, clinical trials demand a centralized resource for data collection and analysis, core laboratories, and support for regulatory issues. These trials may be supported by public or private sponsors, or public-private partnerships. To study a potential therapy requires standardized outcome measures, which must be developed, tested, and validated before they can be utilized in trials. This body of work has been a point of emphasis for the ACR and will continue to be a major area of focus for this organization in the future.

Randomized, controlled trials are considered to provide the strongest evidence of efficacy and safety for a particular pharmacologic or behavioral treatment, but they may not be feasible or ethical in all areas of research in rheumatology. In addition, long-term complications or risks of some therapies are not likely to be detected in most trials because of the limited follow-up time, even for trials lasting 3-5 years. Other quantitative designs as well as qualitative and mixed methods are important approaches for investigating phenomena associated with disease, and the potential benefits of some treatment interventions.

Rheumatologic conditions have a significant impact on health-related and overall quality of life of patients and their families. While the ultimate goal of research is the prevention and cure of disease, investigation is

also needed to mitigate the social, psychological, and economic consequences of a chronic illness. Such research can include epidemiological investigations to examine the many factors influencing disability, such as genetic, cultural, behavioral, and environmental factors; outcome studies evaluating new methods to reduce or prevent pain and disability or otherwise improve quality of life; research in health services to improve patient access and utilization of effective interventions; economic research to determine the true extent and cost of disability; and examination of public policies relevant to these long-term outcomes.

- **Research Process**

Investigations may fall along a continuum encompassing basic, translational, clinical, or health services research. Each component of the research process can exist along a spectrum of small projects to very large-scale, collaborative undertakings. Conventional, small-scale research projects, such as those funded by traditional R01 or P01 grants, will continue to play an important role in the research enterprise. However, the process of research is becoming increasingly complex with a significant growth in large-scale biomedical research. Large-scale biomedical research may include projects that generate masses of related data to accomplish a single goal, the development of a large-scale infrastructure, such as databases and bioinformatics tools, or new technologies to speed research or otherwise realize previously unattainable objectives. Novel approaches to large and complex but focused problems would also fall into this category. By their nature, such large-scale projects are more demanding of expertise and resources and typically require long-range strategic planning, a longer time-frame for completion, a higher total cost, more sophisticated technologies, enhanced research capacity and infrastructure, more oversight by funding agencies, multi-investigator and multi-institutional collaborations, interdisciplinary participation, and extensive data analysis and bioinformatics support. This important part of the research process will require considerable expertise and outlays of new and expensive resources.

## Recommendations for Future Research

- **Support genetic studies and their interpretation to improve understanding of the etiology and expression of arthritis and other rheumatologic diseases**

  - Determine the genetic factors predisposing to disease
  - Analyze the phenotypic variability of disease
  - Determine the role of genes and polymorphisms associated with variations in disease characteristics, including those influencing disease severity
  - Identify novel therapeutic targets based on genetic associations
  - Predict treatment response and adverse events utilizing pharmacogenomics and other genomic applications

- **Support epidemiological studies to improve understanding of arthritis and other rheumatologic diseases**

  - Determine the environmental risk factors for disease, including infectious agents, toxins, occupational exposures, environmental pollutants, and diet
  - Identify sources of gene-environment interactions
  - Identify sociopsychological and behavioral risk factors for disease onset and progression, including the impact of stress on risk of disease and health outcomes
  - Identify the cultural and behavioral risk factors
  - Define the pre-clinical state in more detail to shed further light on disease pathogenesis and evaluate potential treatments aimed at prevention or early intervention
  - Identify the physical, cultural, sociopsychological, and environmental risk factors of disability
  - Utilize pharmacoepidemiology to identify risks associated with drug therapy

- **Improve the understanding of pathophysiology and disease mechanisms**

  - Investigate the regulation of immune and inflammatory pathways and their involvement in disease mechanisms
  - Explore mechanisms of tissue damage in inflammatory and degenerative disease
  - Define mechanisms of vascular injury and angiogenesis
  - Expand knowledge of cartilage and bone biology
  - Elucidate the metabolic abnormalities and other mechanisms associated with crystal deposition diseases
  - Investigate the mechanisms of dysregulated fibrosis and other aberrant tissue repair processes
  - Support biomechanical studies to determine the manner in which the diarthrodial joint may become overloaded and influence the progression of joint disease, including osteoarthritis and inflammatory arthritis
  - Identify mechanisms underlying pain

- **Improve assessment and treatment of rheumatologic disease**

  - Improve assessment of common disease manifestations, including clinically important co-morbid conditions
  - Discover novel biomarkers and imaging modalities for assessing diagnosis and prognosis, especially in the early stages of disease, as well as predicting treatment response
  - Develop creative study designs to evaluate new therapies
  - Investigate innovative methods of drug delivery, including cell-based and gene therapy
  - Investigate innovative theory-driven non-pharmacologic interventions to reduce pain and disability and improve quality of life

- **Support health services research/outcomes research**

  - Investigate efficient, systematic methods to assess patient symptoms and adherence to interventions and to provide timely data for guiding treatment decisions
  - Investigate healthcare models and provider-patient interactions that facilitate patient use of effective interventions that improve function and quality of life, including all forms of self-management (e.g. weight reduction, exercise therapy, pain reduction)
  - Investigate new and improved methods to track and reduce medical errors
  - Investigate new and improved methods to determine the impact of rheumatologic disease and co-morbid conditions on health outcomes

- **Support new research capabilities**

  - Improve access to array, metabolomic, and proteomic technologies
  - Standardize and validate new biomarkers and imaging procedures
  - Develop new animal models to advance understanding of disease mechanisms
  - Create new bioinformatics tools for data analysis
  - Investigate systems analysis to create improved models of immunologic, inflammatory, and metabolic diseases
  - Investigate innovative technology-based methods of therapy assessment and delivery

- **Address needs for new research infrastructure**

  - Establish and expand disease registries
  - Create tissue repositories
  - Develop clinical trial consortia

- **Facilitate the research process**

  - Increase the level of government and private funding as well as industry support
  - Increase the number of early career investigators in all relevant areas of research, including basic science, clinical science, health services, and population health, and ensure the availability of mentors during all stages of career development
  - Stimulate multidisciplinary and inter-professional, focused research initiatives to address complex problems in a way that fosters extraordinary and transforming scientific advances
  - Engage stakeholders, especially patients and the general public, in the research enterprise

## V. List of Participants

Jane Salmon, M.D., Chair, Committee on Research
E. William St. Clair, M.D., Chair, ACR Research Agenda Task Force
Catherine Backman, Ph.D., OTC
Clifton O. Bingham III, M.D.
Michael Brenner, M.D.
Leslie Crofford, M.D.
Alfred Denio, M.D.
Gary Firestein, M.D.
Edward Giannini, DrPH, MSc
Farsh Guilak, M.D.
John Harley, M.D., Ph.D.
Raphael Hirsch, M.D.
Richard Loeser, Jr., M.D.
Carol Oatis, PT, Ph.D.
David Pisetsky, M.D., Ph.D.
Kenneth Saag, M.D., MSc
Elizabeth Schlenk, Ph.D., RN

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