American College of Rheumatology
National Research Agenda
2011 - 2015

This research agenda has been developed and published by the ACR Committee on Research, and is designed to comprehensively address important areas for research in rheumatic diseases including the need for new technology, infrastructure, and increased funding.

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

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I. Executive Summary

Rheumatologic conditions represent a major health burden for 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 providers are represented by the American College of Rheumatology (ACR) and the Association of Rheumatology Health Professionals (ARHP), a division of the ACR. 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, bones, and immune system. ACR membership includes practicing physicians, research scientists, nurses, physical and occupational therapists, podiatrists, physician assistants, biomedical engineers, psychologists, and social workers.

A major goal of the ACR is to promote basic, translational, clinical, and health services research aimed at improving the health of patients with rheumatic diseases. The ACR supports research and education through its annual meetings, publication of its journals *Arthritis & Rheumatism* and *Arthritis Care & Research*, advocacy to increase funding of rheumatology research, and a strong collaboration with its affiliated Research and Education Foundation (REF). The REF advances research and training in rheumatology through its core awards and grants program as well as disease-targeted research initiatives.

The ACR Committee on Research 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 Committee on Research is charged with maintaining a national research agenda. First developed in 2005, the current document represents the first update (2011) of the ACR's Research Agenda, and is intended to comprehensively address important areas for research in rheumatic diseases including the need for new technology, infrastructure, and increased funding.

II. Introduction

Burden of disease

Rheumatologic conditions are a diverse group of disorders that often lead to, physical disability, reduced quality of life, co-morbidities, and early mortality. They also affect the psychological status of individuals and adversely impact social function, career development, school performance, and families. Since many rheumatologic conditions take a chronic or relapsing course, their detrimental effects accumulate over time, leading to a 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., arthritis and other rheumatic conditions affect over 50 million adults (1), approximately 300,000 children (2), and are the most common cause of disability (3). With aging of the population, 67 million adults will have arthritis by 2030, and almost 40% of these people will be limited by their arthritis (4). In the U.S. alone, 27 million people suffer from clinical osteoarthritis commonly affecting the hands, knees, and hips (5). Regional pain disorders are particularly frequent, where more than 59 million people report symptoms of low back pain, and nearly 30 million people have neck pain (5). Fibromyalgia affects an estimated 5 million adults in the U.S. (5).

Many diseases in rheumatology produce acute and chronic inflammation of joints and other tissues. Rheumatoid arthritis (RA), one of the most common causes of chronic inflammatory arthritis, has been estimated to affect nearly 1.3 million individuals in the U.S. (6). RA often culminates in joint damage and disability, and is associated with increased risk of cardiovascular disease and early 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 (7). Spondyloarthritis, comprised of ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthritis affects another 0.6 to 2.4 million adults (6). Gout, another cause of joint inflammation, affects about 3 million people in the U.S. (5). While many of these cases represent acute, self-limited attacks of arthritis, an estimated several hundred thousand patients suffer from either frequent recurrences or chronic gouty arthropathy. For many conditions in rheumatology, women are disproportionately affected. For example, the 0.4 to 3 million adults with primary Sjögren's syndrome are predominately female (6). For systemic lupus erythematosus (SLE), which affects between 161,000 and 322,000 adults (6), the female to male ratio is approximately 10. SLE also has serious systemic effects and results in early mortality, particularly among younger working-age African-American women (8). The prevalence of other conditions may be less well documented, but they nevertheless contribute to the high burden of rheumatologic disease.

Rheumatologic diseases are less common in children than adults, but they are an important group of pediatric diseases because of their chronicity and potentially damaging effects on growth and development. The most common group of childhood rheumatologic disorders is juvenile idiopathic arthritis (JIA), which encompasses several different conditions, including those previously classified as juvenile rheumatoid arthritis (JRA). Most other rheumatic diseases seen in adults also occur in children,

and despite being less common they can have a devastating impact on health. There are wide variations in prevalence estimates for pediatric rheumatic diseases due to differences in nomenclature and geographic distribution. However, recent studies in the U.S. indicate that 403 of every 100,000 children are afflicted with a rheumatic disease, resulting in an estimated 877,000 ambulatory care visits per year (2).

Rheumatologic conditions exert a major toll on patients, families, and society due to their relatively high prevalence in the population. Moreover, many of these conditions are chronic, result in significant pain and disability over the long-term, and are being recognized more frequently as important contributors to cardiovascular disease. Considering the aging, sedentary lifestyle, and the growing epidemic of obesity in the U.S. population, rheumatologic diseases are likely to continue to have a major impact on the health of our population well into the future.

Goals

The ACR seeks 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 recognition of rheumatic diseases and their consequences, more effective management, and better patient outcomes
- Expand funding to increase the breadth and scope of research
- Promote exploration of novel ideas and innovative research methodologies
- Increase access to new research methodologies and technologies
- Foster the development of shared resources including patient registries, biorepositories, and consortia to optimize 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 physician-scientists

III. Methodology

The Board of Directors of the ACR charged its Committee on Research (COR) with revising the 2005 research agenda, hereafter termed the ACR Research Agenda. Dr. Richard Silver was appointed by the Committee Chair, Dr. Robert Colbert to form a Task Force of advisors to assist in this process. Members of this Task Force are listed below in Section V, and include representatives of both the ACR and the ARHP, and adult and pediatric rheumatologists. Initial revisions were made by members of the Task Force, and then edited according to consensus by the COR and Task Force Chairs. The intent of the Task Force was to ensure as much as possible the alignment of multiple perspectives on rheumatology research. After approval by the COR, this document was then sent to the Executive Committee of the Board of Directors for feedback, followed by further editing. 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

A. 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. Genetic predisposition is evidenced by the aggregation of many rheumatologic diseases in families and the association between specific diseases and the presence of certain genotypes. The identification of susceptibility genes is providing more insight into disease mechanisms, and may help to predict prognosis and/or treatment response. 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 is influenced by their genetic make-up, it may also depend on environmental exposures, such as infections, toxins, or diet. 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 patient registries and multidisciplinary epidemiological studies are a way to collect and study this type of information.

Examining the natural processes by which the immune system functions may also shed light on the causes of rheumatologic diseases that are autoimmune or autoinflammatory in origin. Autoimmune diseases occur when the adaptive 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 silenced or "tolerized", either by elimination, inactivation, or regulation. In contrast to autoimmunity, autoinflammatory diseases occur when the innate immune system is repeatedly or continuously activated in the absence of self-reactive antibodies or T cells. While some rheumatic diseases fall clearly into autoimmune or autoinflammatory categories others may represent a mixture of both processes. Understanding the regulation and interaction of both innate and adaptive immune processes in normal and disease states is vital to elucidating the mechanisms involved in rheumatic disease.

B. Mechanisms of Disease

Much research has focused on the pathogenic mechanisms involving immunity and inflammation. In arthritis research, for example, investigation of both animal models and patients has deepened considerably our understanding about the roles of the innate and adaptive immune systems in causing joint inflammation and damage. These studies have led to the identification of a number of therapeutic targets, such as tumor necrosis factor (TNF)-a and interleukin (IL)-1 and IL-6, leading to major advances in patient care. These findings have translated into therapeutic breakthroughs for diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and the autoinflammatory syndromes. More recently, discovery of the IL-23/IL-17 axis and its importance in several immune-mediated

inflammatory diseases, together with evidence that several susceptibility genes lie in this pathway, has pointed toward promising new targets for therapeutic intervention. Advances have also been made in understanding the role of innate effector responses in the pathogenesis of diseases such as SLE and crystal-induced arthritis, and complement activation has been shown to play a key role in the recurrent miscarriages associated with anti-phospholipid antibody syndrome. Studies suggest that monitoring of certain products of the complement system may serve as tools for improving diagnosis, measuring disease activity, assessing prognosis, and determining response to therapy. New insights have also been 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.

Significant advances are emerging from large genome-wide association studies revealing the complexity of genetic susceptibility to rheumatic diseases. These studies have implicated new mechanistic pathways in the pathogenesis of diseases such as SLE, RA, ankylosing spondylitis, and Behçet's disease, and are bringing new therapeutic targets into focus. Genetic epidemiology studies also have the potential to clarify the basis for racial and ethnic differences in disease incidence, severity, and response to therapy.
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.

C. 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 determine whether there is a therapeutic effect of the experimental treatment and to detect toxicity.
Treatments determined to have a clinical benefit can be further tested in effectiveness trials. These studies include a wider range of patients (e.g. greater age range, presence of co-morbidities, etc.) that better simulate a typical clinical practice. Such studies might also compare, for example, usual clinical care (e.g. a pharmaceutical intervention) to usual care plus structured behavioral interventions (e.g. education, self-management, exercise, and weight loss), as well as investigating the coupling of clinical

care with community-based interventions. Comparative effectiveness research can provide key information for clinical practice decision making by identifying the best treatments, either single or in combination, that are most effective and for which patients.

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, including successful production of pluripotent stem cells from reprogramming fibroblasts and hematopoietic cells (induced pluripotent stem cells or iPSC), significant challenges remain to successfully translate cell-based technologies into viable, safe treatment strategies. Solving this complex problem requires multidisciplinary approaches and the cooperation of cell and molecular biologists, bioengineers, biomaterials experts, orthopedic surgeons, and rheumatologists.

Because of their collaborative nature, large 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, as evidenced by the recent special issue of *Arthritis Care & Research* devoted to patient outcome measures (9). Identifying and utilizing standardized outcome measures 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 may not be detected in these trials because of limitations in follow-up time and the number of subjects studied. 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 disease incidence and disability, such as genetic, cultural, behavioral, policy, 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 evaluation of public policies relevant to these long-term outcomes.

In recognition that there are significant gaps in our knowledge surrounding the clinical care of patients with RA, the ACR formed a Task Force to address issues related to trial design and to establish priorities for future clinical trials (10).

D. Research Process

Investigations fall along a continuum encompassing basic, translational, clinical, health services, and community-based research. Each component of the research process can exist along a spectrum of small projects to large-scale, collaborative undertakings. Conventional, small-scale research projects, such as those funded by traditional private foundations, and investigator-initiated NIH R01 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 projects that generate masses of related data to accomplish a goal. This requires the availability of large-scale infrastructure, including databases and bioinformatics tools, and the development of new technologies to store and manage data and accelerate research to realize previously unattainable objectives. 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. As an example, genetics research often requires pooling of available cohorts to achieve the sample sizes necessary to detect and then replicate the many small genetic effects that together create disease susceptibility and influence severity. Similarly, clinical/observational research projects are enhanced by collaborative sharing of data providing substantially larger cohorts than present at one institution. These important parts of the research process require substantial expertise and demand considerable resources.

E. Recommendations for Future Research

- **Support genetic studies and their interpretation to improve understanding of the etiology and phenotypic expression of arthritis and other rheumatologic diseases**
  - Determine the genetic factors predisposing to disease, including common and rare polymorphisms, and copy number variants
  - Determine genetic factors responsible for phenotypic variation including disease severity, other organ involvement, response to therapy, and risk of infection and malignancy
  - Identify novel pathogenic pathways and potential therapeutic targets implicated by genetic associations
  - Establish genotypes that predict treatment response and adverse events utilizing pharmacogenomics
  - Determine the role of epigenetic modifications and somatic mutations in disease

- **Support epidemiological studies to improve understanding of arthritis and other rheumatologic diseases**
  - Determine intrinsic and extrinsic risk factors for disease onset and progression, including diet, microbes, toxins, occupational exposures, environmental pollutants, cultural influences, personal characteristics, and behaviors
  - Identify epidemiologic risk factors influencing disability and early mortality
  - Identify gene-environment interactions, particularly risk factors that can be modified to reduce disease risk and improve response to treatment
  - Identify underlying causes of disparities in treatment, outcome, and early mortality
  - Better define the natural history of the less common rheumatic diseases, including the temporal onset of other co-morbid conditions and their effect on disease incidence and outcomes
  - Utilize pharmacoepidemiology to identify risks associated with drug therapy
  - Define the long-term risk of disease burden and treatment on children with rheumatic disease
  - Increase cost effectiveness research

- **Define mechanisms of disease pathogenesis**
  - Investigate the regulation of immune and inflammatory pathways and their involvement in disease mechanisms
  - Determine functional importance of disease susceptibility alleles to gain insight into disease mechanisms and fundamental biological processes
  - Investigate preclinical disease states to inform understanding of pathogenesis
  - 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, bone formation, 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 normal and aberrant pain sensing

- **Improve assessment and treatment of rheumatologic disease**
  - Define preclinical disease states to enable evaluation of early intervention and secondary prevention strategies
  - Improve assessment of common disease manifestations, including clinically important co-morbid conditions, to design effective risk management strategies, appropriate monitoring, and evidence-based early interventions
  - Discover and validate novel biomarkers and imaging modalities for assessing diagnosis and prognosis, especially in the early stages of disease, as well as predicting and monitoring treatment response

- **Improve assessment and treatment of rheumatologic disease (continued)**
  - Develop innovative study designs to evaluate new therapies
  - Conduct comparative effectiveness studies to evaluate combined pharmacological and behavioral interventions
  - Employ large-scale systems approaches with well-defined phenotypes and qualified biomarkers to model disease, enabling development of efficient clinical trial designs and informed clinical decision-making
  - 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 and systematic methods including validated patient reported outcomes, 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 interventions that improve function and quality of life, including all forms of self-management
  - 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
  - Address issues such as pain, fatigue, psychosocial adjustment, physical functioning, and intervention strategies in pediatric rheumatic disease patients
  - Investigate the variability in patient outcomes related to differences in behavior, gender, ethnicity, family development, prior trauma, education, physiology, or a combination of factors
  - Evaluate the outcomes of clinical preventive services such as influenza and pneumococcal vaccination, and cancer screening, on morbidity and mortality among patients with inflammatory rheumatic disease
  - Examine practice patterns to better inform strategies that will increase access to rheumatology services
  - Conduct studies of adherence to evidence-based clinical practice guidelines and quality-of-care metrics

- **Support new research capabilities**
  - Ensure access to microarray, metabolomic, immunophenotyping, and proteomic technologies, and bioinformatics support
  - Increase access to next-generation sequencing technology for whole exome and whole genome sequencing, RNA-seq, and epigenetic analyses
  - Standardize and validate new biomarkers and imaging procedures, including human immunophenotyping and in vivo imaging of immune function
  - Establish induced pluripotent stem cell lines (iPSC) from patients with rheumatic disease to study disease-relevant cells and tissues
  - Develop cell-based therapies for the treatment of rheumatic diseases

- **Support new research capabilities (continued)**
  - Develop new animal models to advance understanding of disease mechanisms
  - Create new bioinformatics tools for data analysis
  - Develop a fast track mechanism for phase I (first in human) trials for therapies directed at rheumatic diseases
  - Explore extramural-intramural collaborations that utilize the NIH Clinical Center
  - Investigate systems analysis to create improved models of immunologic, inflammatory, and metabolic diseases
  - Investigate innovative technology-based methods of therapy assessment and delivery including pharmacogenetics
  - Initiate and evaluate successful models of clinical and community collaborative care for persons with rheumatic disease
  - Develop social media as a tool to enhance subject recruitment and retention for clinical and translational studies

- **Address needs for new research infrastructure**
  - Establish and expand disease registries. Explore new opportunities to collect clinical data using innovative electronic medical records and internet-based registries that capture a broader range of patients
  - Create biorepositories with a broad range of specimens linked to registries with detailed clinical data that will facilitate translational research
  - Develop clinical trial consortia. Establish networks of investigators with a common disease interest and cadres of patients available for trial enrollment
  - Create infrastructure for meaningful studies of preclinical rheumatic disease

- **Facilitate the research process**
  - Increase government and private funding as well as industry support
  - Increase the number of early career investigators in all relevant areas of research, including basic, translational, and clinical science, health services and outcomes, and population health, and ensure the availability of committed mentors during all stages of career development
  - Support the academic pipeline of investigators in the rheumatic diseases
  - Stimulate multidisciplinary and inter-professional, focused research initiatives to address complex problems in ways that foster extraordinary and transforming scientific advances
  - Engage stakeholders, especially policymakers, patients and the general public, in the research enterprise

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VII. About the ACR

The American College of Rheumatology is an international professional medical society that represents more than 8,000 rheumatologists and rheumatology health professionals around the world. Its mission is to advance rheumatology.

The College is for physicians, health professionals, and scientists that meets the mission through programs of education, research, advocacy and practice support.

The ACR provides professional education for its members through several venues. The Annual Scientific Meeting, held each fall, is the premier scientific meeting devoted to the rheumatic diseases. This meeting draws thousands of rheumatologists and arthritis health professionals from around the world. A winter rheumatology symposium, spring clinical meetings, and other topical conferences round out the ACR's educational offerings.

The ACR publishes *Arthritis & Rheumatism*, the premier scientific journal for research in the rheumatic diseases. *Arthritis Care & Research* is published by the Association of Rheumatology Health Professionals, a division of the ACR. This journal focuses on the health services and clinical aspects of rheumatology.

For more information about the ACR, please visit www.rheumatology.org.

American College of Rheumatology
2200 Lake Boulevard NE
Atlanta, Georgia 30319
(404) 633-3777
www.rheumatology.org