NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS)

LONG-RANGE PLAN: FISCAL YEARS 2006-2009

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1) INTRODUCTION

The NIAMS supports basic, translational and clinical research, research training, and information programs on many of the more debilitating diseases affecting the American people. Most of these diseases are chronic and many cause life-long pain, disability, or disfigurement. They afflict millions of Americans, cause tremendous human suffering, and cost the United States economy billions of dollars in health care and lost productivity. These diseases include the many different forms of arthritis and numerous disorders of the musculoskeletal system and the skin. The Institute also conducts and supports research on the normal structure and function of joints, muscles, bones, and skin. The purpose of this long-range plan is to serve as a broad scientific outline for the NIAMS, and for the investigative and lay communities, by identifying compelling research opportunities that will inform the Institute's priority-setting process. We acknowledge that the plan is not comprehensive and that not all research areas were able to be addressed. Over time, this long-range plan will help propel research progress related to the understanding, diagnosis, treatment and, ultimately, prevention of arthritis, musculoskeletal and skin diseases.

2) CROSS-CUTTING AREAS

One of the major strengths of the NIAMS research program is its "cross-cutting" nature -- research that cuts across many disciplines and involves the interplay and collaboration of a diverse array of specialists from both basic and clinical areas. These multidisciplinary fields of research cut across all areas of the NIAMS, and indeed, much of the National Institutes of Health (NIH). Collectively, they reveal the broad, diverse, interdisciplinary mandate of the NIAMS and are integral components of all our programs.

Two cross-cutting areas with strong NIAMS commitment are health disparities research and research training. These areas are not discussed in detail in this document as more specific details on these efforts may be found by viewing the NIAMS Strategic Plan for Reducing Health Disparities (http://www.niams.nih.gov/an/stratplan/index.htm) and the NIAMS and NIH-wide efforts to support biomedical research training (http://www.niams.nih.gov/rtac/index.htm and http://grants1.nih.gov/training/).

2A) BEHAVIORAL AND BIOPSYCHOSOCIAL RESEARCH IN ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Behavioral and social factors are involved in numerous ways in the onset, course and outcomes of chronic diseases. These factors are central in the experience of symptoms (such as pain and fatigue), disease-related distress, and coping with chronic disease, disability and, to varying extents, the

success of prevention and treatment approaches. In addition, interactions between the immune and central nervous systems may be relevant to autoimmune diseases within the NIAMS mission but have not been well-studied.

Purely biomedical approaches are not sufficient to understand and optimally manage the chronic diseases within our mission. Interdisciplinary research that integrates behavioral and biomedical sciences is likely to result in enhanced management of these diseases and reduced disability, and may shed light on the complex mechanisms involved in these disease processes. Biopsychosocial research needs in rheumatic, musculoskeletal, and skin diseases include:

- Studies of biological mechanisms of psychosocial or behavioral processes related to disease onset, progression, and outcomes; of genetic and environmental influences on behaviors relevant to health; and of neuroimmune and neuroendocrine pathways.

- Studies on non-pharmacological interventions and combined interventions, including development and testing of individual, group, and technology-based interventions to enhance self-management and improve health-related behaviors; research on tailoring interventions based on disease phenotype, individual psychological or social characteristics, and cultural/ethnic considerations; and educational and related interventions to enhance prevention.

- Development and testing of early interventions involving family members and addressing psychosocial issues.

- Studies to determine how to disseminate information effectively to target audiences and how to translate knowledge into behavioral change, including studies of factors that influence decisions about adopting and adhering to treatment and preventive interventions.

- Studies investigating variability in patient outcomes. Individuals differ tremendously in their response to clinical disease and symptoms. Reasons for this variability are not well understood and may include biological factors, behavioral differences, sex differences, ethnic background, family environment, previous trauma, education, or a combination of factors.

- Studies on management of chronic symptoms such as itch, fatigue, parethesias and pain, and of management outcomes. Develop and test more valid, reliable, efficient measurement instruments and methodology to measure symptoms and health-related quality of life variables important to patients.

2B) BIOMARKER (BIOCHEMICAL, GENETIC, AND IMAGING) IDENTIFICATION, MEASUREMENT, AND VALIDATION FOR ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Many of the diseases at the core of the mission of NIAMS are chronic and have long, variable clinical courses. These diseases take decades to develop and progress and, they are difficult to characterize. It is also challenging to predict responses to treatments when such treatments are available. The development of novel therapies to prevent or delay disease progression and the prediction of those who will or will not respond to treatments are common goals for NIAMS, the Food and Drug Administration, and industry. However, therapies to prevent, delay, or ablate many of these diseases have not been brought to market, despite major advances in understanding of the disease, in large part because of the inability to accurately measure disease progression and response to therapies.

Clearly, with many disorders, a battery of biomarkers rather than a single biomarker may provide the most clinically useful information, and development of multiplex assay systems will be critically important. In general, these markers of disease, responses to treatment, and abilities to respond are measured by changes in biochemical factors in blood or bodily fluids or genetic biomarkers in tissues or peripheral blood cells. However, in addition to biochemical and genetic markers of disease and response to therapy, the capability to image early or late changes of disease in end organs becomes increasingly important for characterization of disease status and responses to therapies.

Efforts to produce these imaging changes may lead to creation of direct and sensitive tissue-specific markers. Broad, innovative use of imaging techniques could enable early identification of disease onset, predict disease progression, and make possible direct monitoring of responses to therapeutic interventions. Thus, biomarker development presents an institute-wide, crosscutting area of interest for NIAMS. While disease-specific needs are highlighted in each of the programmatic areas of the Plan, there are some overarching needs that are shared in the NIAMS mission areas. The broad goals for these areas are highlighted below:

- Create the resources required to move promising biomarkers from the bench to the clinic using state of the art statistical, analytical, and computational methods.

- Encourage broad use of the existing repositories and databases for the discovery and validation of biochemical and structural changes associated with onset and progression of diseases of interest to NIAMS.

- Develop new or enhanced relationships with biostatistical core resources to assist investigators engaged in biomarker development and validation.

- Broaden biomarker investigations to include genetic or biomechanical markers of disease or markers that may predispose individuals to heightened risk of disease progression/worsening/severity or predict responses to treatments.

- Develop and apply new technologies for the discovery of biomarkers of disease onset, progression, and response to therapy.

- Develop biomarkers that will be useful for predicting overall outcomes or outcomes in specific subsets of patients.

- Link studies of novel therapeutic agents used in the treatment of rheumatic, musculoskeletal, and skin diseases with mechanistic studies that could identify useful biomarkers.

- Encourage basic exploratory studies to identify lead candidate biomarkers.

- Encourage the development of validated and standardized outcome measures to enable better assessment of biomarkers and success of interventions.

- Apply existing and newly developed imaging technologies to improve understanding of disease, and to enable identification of possible imaging biomarkers associated with disease onset and progression.

- Promote exploratory and more focused clinical research applying non-invasive imaging technologies to functional studies of disease prognosis and disease course.

2C) CLINICAL RESEARCH IN ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Clinical studies ranging from epidemiological studies, observational studies and clinical trials play a valuable role in carrying out the mission of the NIAMS. Clinical research and basic research contribute synergistically to the advancement of knowledge about rheumatic, musculoskeletal, and skin diseases, and translational research is where bench science meets the bedside. Many improvements in the quality of life of individuals with arthritis and musculoskeletal and skin diseases have resulted from clinical investigations and clinical trials. The future holds many exciting opportunities

for advances in clinical investigations, clinical trials and clinical outcome measure validation. Clinical research needs common to rheumatic, musculoskeletal, and skin diseases include:

- Epidemiological studies related to the demographics of the population including age, gender, co-morbidities, and ethnic and racial diversity, for conditions and diseases within the mission of NIAMS.

- Prevention studies focused on identification of risk factors and risk reduction strategies.

- Early intervention trials to prevent onset or progression of disease or injury.

- Studies that implement and evaluate innovative therapies, treatments, or technologies.

- Exploration of efficient diagnostic testing and treatments for genetic diseases.

- Research that builds on the NIAMS investment in burden of disease studies.

- Clinical trials that measure efficacy through the use of validated, standardized outcome measures.

- Encouragement of the utilization of existing resources such as repositories and databases in the design of clinical studies.

- Access to large databases to answer questions of utilization and access to care.

- Promote the development of computer models to assess the influence of prevention and treatment strategies on outcomes and cost effectiveness in common chronic diseases (e.g., osteoarthritis, rheumatoid arthritis and osteoporosis).

- Clinical research on combination therapies.

- Clinical trials related to the cause and treatment of system-specific pain.

- Expand the involvement of clinical practice physicians in community settings, in large-scale trials.

2D) COMPLEX GENETIC INFLUENCES IN ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Complex functions of genetic characteristics influence the risk that an individual will develop a disease and affect the onset time and severity of the disease, and even the response to therapy. In addition to predicting disease risk and response to therapy, identification of genetic factors underlying disease can also suggest new therapeutic targets. Resolving such complex genetic influences presents many technical challenges. However, the potential for health benefit is very significant, because many diseases that are likely to be subject to complex genetic influences are relatively common in the population.

With the availability of the human and mouse genomic sequences, and the development of powerful tools for manipulating genes in mice, our understanding of the biological function of individual genes is advancing at a rapid pace. Recently, much progress has been made in determining how human genes vary from one individual to another. The simplest types of genetic variation, called single nucleotide polymorphisms (SNPs), have now been cataloged at hundreds of thousands of chromosomal sites in people from all over the world, defining units of variation called haplotypes. This information has been combined into a resource called the Haplotype Map or HapMap. Technology has been developed that allows for the rapid and economical assessment of haplotypes in people. Taken together, these advances offer both great opportunities and great challenges.

Current studies and the emerging availability of well characterized human cohorts and animal models suggest that work on the discovery of genes and their function in disease is now feasible. The analysis of complex genetic influences could shed new light on many diseases within the NIAMS mission, including rheumatoid arthritis, systemic lupus erythematosus (lupus), osteoporosis, osteoarthritis, and psoriasis. Taking full advantage of this potential will require efforts in a number of complementary areas, including:

- Assemble large, well-characterized collections of cases and matched controls. In some cases, it may be possible to adapt existing cohorts to genetic studies.

- Investigate the role of genetic influences in determining disease susceptibility. It may be possible to address some diseases at the level of whole genome association studies, which have the potential to detect all significant genetic influences on a given phenotype.

- Explore the contribution of gene-gene interaction and gene-environment interaction to the overall genetic influence on disease susceptibility.

- Explore the feasibility of establishing shared resources, linking phenotypic and genotypic data in formats that will facilitate novel analytical approaches and collaborative investigations. This may be particularly important in order to focus the full power of developing bioinformatics methodology on problems of interest to the NIAMS.

- Study the pharmacogenomics of responders and non-responders to pharmacologic and biological interventions, in order to direct therapies to the appropriate patient subsets.

- Explore the integration of genetic analysis and molecular diagnosis with clinical care.

- Pursue complex genetic analyses in mice. Common inbred mouse strains represent significant genetic and phenotypic variation. Quantitative trait locus (QTL) analysis shows promise in detecting genetic influences on many important physiological parameters. The identification of QTLs in mice can be an important guide to studies in humans.

2E) IMMUNOLOGY IN ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

The immune system consists of a complex and dispersed set of organs, thymus, spleen, lymph nodes, and bone marrow, as well as the defensive barriers such as the skin and mucosal surfaces and a complex and dispersed set of freely moving cells from the bone marrow, blood and lymphatic system. Two arms, innate and adaptive immunity, long thought to be separate, are now known to exist in a delicate balance with constant interaction. The innate immune system, which is a nonspecific response to injury, inflammation and infection, has rapid response kinetics but lacks memory. This arm involves effector cells (natural killer cells, gamma delta T cells, plasmacytoid dendritic cells, macrophages, mast cells, neutrophils), cellular receptors (Fc receptors, complement receptors, scavenger receptors, Toll-like receptors), effector proteins (complement, mannose binding lectin, C-reactive protein, coagulation factors), and cytokines (TNF, Interleukin (IL)-1, Interferon (IFN)-gamma, IFN alpha and beta, IL-15 etc.).

In adaptive immunity, which includes T and B lymphocytes and dendritic cells, the response kinetics are slow, but specific. T and B cells recognize the pathogen, and memory is developed to respond more rapidly to a future infection. Surveillance for infection and tissue injury occurs via immune cells that are resident in organ tissues, and immune cells that traverse the body tissues via the cardiovascular and lymphatic systems. Immune cells interact with each other and organ tissue cells in a cell-to-cell manner via receptors

and receptor ligands. Local and long distance communication is also involved via chemicals such as hormones, cytokines, chemokines and their respective receptors. The interrelated functions of protecting injured tissues from infection and providing for tissue maintenance and repair of injuries, puts the immune system in constant interaction with bone, muscle, skin and joint tissues.

It remains a mystery why, in some people, the immune system comes to recognize components of the body as foreign and targets those tissues for attack. Such immune dysregulation results in autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjogren's syndrome, spondyloarthropathies, polymyositis and dermatomyositis as well as rheumatic/inflammatory manifestations associated with HIV infection and AIDS, all of the juvenile rheumatic diseases, and a plethora of skin diseases, including pemphigus, pemphigoid, psoriasis, and many others.

The structural and functional properties of target organs and responses of target organ tissue to tissue damage may significantly contribute to further tissue damage and clinical disease. For example, tissue responses to self-protein autoantibodies may activate tissue cells, which can modify cell function or induce apoptosis (programmed cell death). These events can result in the expression of developmental proteins, intracellular proteins, or apoptotic blebs on the surface of cells that can intensify the self-protein and tissue activation responses. Recent studies suggest that proteins expressed on regenerating muscle cells in myositis may enable such a feed-forward loop of tissue damage. Also, autoantibodies in lupus nephritis cross-react with the intracytoplasmic molecule, alpha-actinin.

On the other hand, under inflammatory conditions, some pathological bone resorption may, in part, be due to interactions between activated T cells and osteoclasts. Recent work indicates that bone and possibly skeletal muscle and the immune system share some of a complex network of cytokines and molecular mediators that regulate function and homeostasis. Better understanding in normal and pathological situations of interactions between the immune system and bone, muscle, skin and joint tissue will lay the groundwork for future therapies for diseases within the NIAMS mission.

While disease-specific needs are highlighted in each of programmatic areas of the Plan, there are some over arching needs that are shared in the NIAMS mission areas. The broad goals for these areas are highlighted below:

- Study the interrelationships between the immune response components and regulatory and structural components of cartilage, bone and muscle in health and disease.

- Develop new animal models and encourage the use of already developed transgenic animals, knock-out animals and knock-down

methods to understand the immune and inflammatory mechanisms of organ damage.

- Develop new animal models to differentiate between autoimmune mechanisms and mechanisms of target organ damage from autoimmunity (i.e. cutaneous lupus).

- Establish the type and mediators of interactions of the innate and adaptive immune systems in the initiation and amplification of inflammatory and autoimmune disease (i.e., the role of innate immunity in activating adaptive immunity).

- Explore the role of specific cytokines, chemokines, eicosanoid (and other lipid mediators), proteases (including the neutral proteases from mast cells), inhibitors of proteases, as well as receptors for these molecules in the autoimmune and inflammatory components of NIAMS diseases.

- Define the cellular and molecular mechanisms that downregulate/terminate the inflammatory response beyond T cells.

- Study the role of B cells and plasma cells and their potential value as therapeutic targets.

- Promote improved understanding of common immune-mediated mechanisms of disease to develop “common therapies.”

- Study the pathophysiology of the biologic agents used currently to treat rheumatic and autoimmune conditions to learn more about their implications for skin and muscle disease treatment.

- Study the mechanisms of tissue damage and fibrosis including oxidative stress mediators.

- Study the mechanisms of comorbidities of connective tissue diseases.

2F) REGENERATIVE MEDICINE

Regenerative medicine -- which includes tissue engineering and gene, cell and pharmacological treatments that restore tissue structure and function -- is a rapidly growing multidisciplinary field involving the life, physical and engineering sciences. The field seeks to develop functional cell, tissue, and organ substitutes to repair, replace or enhance biological function that has been lost due to congenital abnormalities, injury, disease, or aging. It includes both the regeneration of tissues *in vitro* for subsequent implantation

in vivo as well as direct *in vivo* tissue regeneration. In addition to having a therapeutic application, tissue engineering can have a diagnostic application where the engineered tissue is used as a biosensor. Engineered tissues can also be used for the development of drugs including screening for novel drug candidates; identifying novel genes as drug targets; and testing for drug metabolism, uptake, and toxicity.

Regenerative medicine includes the following areas: (1) development of novel biomaterials/scaffolds including biomaterials that are designed to direct the growth, differentiation, and organization of cells in the process of forming functional tissue by providing physical, chemical, and mechanical cues; and (2) identification of optimal cell sources, including the acquisition or modulation of appropriate cells for particular applications from a variety of potential sources such as autologous, allogeneic, syngeneic, and xenogeneic cells, stem and progenitor cells, and genetically engineered cells. The methods that deliver the cells to the tissue and the approaches that direct cells to the appropriate tissue location are important as well. Also included are methods for the directed proliferation and differentiation of cells and immunological manipulation. The NIAMS believes that regenerative medicine offers exciting opportunities for the repair and/or direct replacement of damaged, diseased, or missing musculoskeletal tissues and skin.

The following are some of the important research needs and opportunities in this area:

- Identify and encourage coordinated approaches to tissue regeneration that are informed by both the biology research community and the tissue-engineering research community. It is important for researchers to explore regeneration in the context of dynamic and complex systems of intracellular and intercellular communication and change.

- Develop hybrid models to study diseases for which no good model systems exist. *Hybrid model* refers not to a genetically altered mouse model but to a bioengineered artificial construct in which diseased human tissue is transplanted in an animal host that has been modified to accept the foreign tissue. Hybrid models open a new avenue of hypothesis-driven research for a number of diseases for which other good models do not exist. Hybrid models also provide a means for studying potential treatment interventions or gene therapies.

- Determine the heterogeneity, organizational hierarchy, and intrinsic biologic behavior and potential of stem cells and progenitors.

- Identify modulators for stem cell activation, proliferation, migration, homing, differentiation, integration and survival.

- Identifiy markers for stem cell populations, transit populations, and progenitors useful for *in-vitro* and *in-vivo* assay.

- Determine signaling pathways that control cellular proliferation, differentiation and survival in cells of mesenchymal origins.

- Enhance understanding of regulatory regions of genes relevant to musculoskeletal tissues and skin.

- Ability to engineer scaffolds with complex, controlled architecture and targeted sets of physical and mechanical properties.

- Develop novel strategies for scaffold surface modification to promote cell adhesion, tissue integration, and control cellular phenotype.

- Encourage the use of recombinant technologies for control of biomaterial, design, synthesis, and assembly.

- Improve delivery systems controlling conformation, presentation, concentration, delivery rate, bioavailability, and distribution of growth factors and cytokines.

- Establish biomechanical and biophysical parameters of requirements for successful tissue engineered constructs.

- Develop and/or validate modalities to: (1) image tissue cellular morphology, function, and chemistry *in situ,* including cell tracking; and (2) non-invasively determine the success/outcome of tissue-engineered repairs.

- Develop and validate appropriate animal models.

- When available, develop clinical studies to assess the efficacy and effectiveness of tissue-engineered repairs.

2G) RESEARCH INFRASTRUCTURE

Investigators are encouraged to propose, develop and utilize research infrastructure that will accelerate progress and make efficient use of investments in research. Research infrastructure is expensive and time-consuming to develop and maintain, so it is imperative that researchers stay informed about and have access to the products of NIAMS-funded infrastructure initiatives. Many infrastructure-support mechanisms are being developed through the NIH Roadmap for Medical Research. NIAMS-funded investigators are encouraged to utilize these resources.

Some broad recommendations include:

- Encourage the development of shared core resources including the state-of-the-art new technologies and instrumentation.

- Coordinate development and characterization of animal models for diseases and disorders: optimize genetic background, standardize outcome measures, increase availability of models and sharing of data. Expand the use of other model systems such as zebrafish and invertebrates, where advantageous.

- Expand and intensify research collaborations and communication between disease-focused research centers, medical research centers and patient care communities

- Characterize resources and information and increase their availability and utilization by investigators by networking existing registries and repositories and linking them to data sets such as the MD STARnet project supported by the Centers for Disease Control and Prevention.

- Expand molecular infrastructure including cell and molecular libraries, gene and protein expression profile databases and analysis tools, and clinical databases.

3) TISSUE AND DISEASE-SPECIFIC AREAS

In addition to the cross-cutting fields of research described above, the NIAMS supports a robust program of studies in tissue and disease-specific areas. These include investigations in rheumatic, musculoskeletal, muscle, and skin diseases research, as well as studies aimed at enhancing our understanding of the normal structure and function of joints, bones, muscles, and skin. The following sections describe promising scientific opportunities in these areas, as well as pressing public health needs that NIAMS seeks to address.

3A) RHEUMATIC DISEASES RESEARCH

Supporting high-quality basic, translational, and clinical research is key to treating, curing, and preventing rheumatic diseases. This includes work that advances the understanding of the natural history of these disorders, as well as mechanisms of disease susceptibility and disease development. A critical dimension of this effort involves taking advantage of new insights in the fields of genetics, genomics, and proteomics related to rheumatic diseases. The

NIAMS is also committed to pursuing new opportunities to identify risk factors for these disorders, to enhance disease prediction and prevention strategies.

Highlights of research needs and opportunities include:

3A-1) Genetics and Genomics

Discoveries pertaining to the genetic contribution to immune and inflammatory disorders continue at a rapid pace. New mutations in genes in humans and in mice that result in immune disorders are identified routinely. Coupled with advances in genomics and the elucidation of gene polymorphisms, these discoveries present tremendous opportunities and tremendous challenges. The discovery that a gene that encodes a particular enzyme (PTPN22) is associated with rheumatoid arthritis, systemic lupus erythematosus (lupus), thyroiditis, and type I diabetes illustrates the relevance of this approach. The approach of screening cohorts with candidate SNPs (single nucleotide polymorphisms – a small genetic variation that can occur within a person's DNA sequence) can yield valuable insights into disease etiology. How do we best take advantage of this information? How and when do we incorporate advances in genetics and genomics with clinical care and treatment? The following are highlights of promising areas of research:

- Investigate/identify disease and disorder-specific genes and their products determining disease susceptibility.

- Identify allelic variants contributing to disease susceptibility in the general population. The discovery of genetic abnormalities contributing to the various phenotypes of rheumatic diseases may be enhanced through more precise phenotyping and by association studies. This will require the assembly of large, well-characterized (clinically, serologically, and immunologically) collections of cases and matched controls.

- Identify the genes shared by various autoimmune disorders and exploration of their interactions.

- Use large, well-defined cohorts of patients, to identify polymorphisms and disease associations, and follow-up studies with high-density mapping using SNPs.

- Mine whole genome data for application to autoimmune and rheumatic diseases within the mission of the NIAMS.

- Study how human gene mutations that primarily affect innate immunity are associated with autoimmune and autoinflammatory diseases.

Similarly, explore the interaction between genes associated with immunodeficiency and autoimmune diseases in disease susceptibility.

- Conduct exploratory discovery-driven experiments with genomics and proteomics in diseases including scleroderma, myositis, polychondritis, etc., using a limited number of readily available patient samples linked to good clinical data and appropriate biostatistical approaches.

- Investigate genetics and functional genomics to discover mechanisms of rheumatic diseases in children.

- Expand approaches that facilitate investigators sharing information on autoimmune diseases or cancer in general and its application to rheumatic diseases.

- Link developments in genomics, proteomics, bioinformatics, and systems biology to clinically relevant issues, particularly prediction, prevention, and monitoring of rheumatic diseases. Define assays that are effective at monitoring disease activity and that predict the development of specific complications.

- Study the pharmacogenomics of responders and non-responders to pharmacologic and biological interventions in rheumatic diseases to direct therapies to the appropriate subsets of patients.

- Characterize and define the role of epigenetic mechanisms in the onset and progression of rheumatic diseases.

3A-2) Mechanisms of Disease

Since there has been dramatic progress in developing molecular and genetic tools for basic research, we can now begin to address disease-specific pathogenic mechanisms. Targeted disease-specific investigations of the inflammatory arthritides have a high likelihood of producing findings that translate to clinical practice. Specifically, *in vivo* animal model research on inflammatory arthritis utilizing molecular and genetic approaches to identify critical cellular and molecular mediators of inflammation may lead to the identification of targets for intervention in these diseases. Highlights of areas of special interest include:

- Promote cross-disciplinary studies that investigate the links between inflammation, metabolic diseases and rheumatic diseases.

- Establish the type and mediators of interactions of the innate and adaptive immune systems in the initiation and amplification of

autoimmune diseases (i.e., the role of innate immunity in activating adaptive immunity).

- Further define the role of regulatory T cells and cytokines in reducing autoimmune responses.

- Define the cellular and molecular mechanisms that downregulate/ terminate the inflammatory response beyond T cells.

- Elucidate the effector mechanisms of tissue damage (e.g., complement, FcR, and cytokines).

- Explore the role of specific cytokines, chemokines, eicosanoids (and other lipid mediators), proteases (including the neutral proteases from mast cells), and inhibitors of proteases, as well as receptors for these molecules in the arthritic and inflammatory components of related diseases.

- Dissect the mechanisms regulating recruitment, maturation, activation, effector function, and regulation of apoptosis of synovial macrophages, lymphocytes, mast cells, dendritic cells, neutrophils and fibroblasts, and their role in perpetuation of diseases.

- Define the mechanisms that control the development and retention of mast cells in the rheumatoid joint and the mediators released from activated mast cells that promote joint injury.

- Develop analytic methods and mechanism-directed analyses of ex-vivo synovial specimens from patients with rheumatoid arthritis and other inflammatory arthritides.

- Study the interaction between the immune system and bone (e.g., osteoprotegerin, RANKL, etc.).

- Study the etiology and mechanisms of rheumatic muscle disease and damage, particularly mechanisms of myositis and muscle weakness and dysfunction in other rheumatic diseases (e.g., scleroderma, systemic lupus erythematosus, and rheumatoid arthritis).

- Expand the understanding of autoantigen expression in rheumatic diseases, focusing particularly on autoantigens in rheumatoid arthritis, and the role of metabolic and other changes in the joint environment that result in the generation of autoantigens.

- Investigate the role of cell de-differentiation and the effects of impaired maintenance of a differentiated state on onset and target organ damage.

- Develop new animal models to differentiate between autoimmune mechanisms and mechanisms of target organ damage from autoimmunity and, to test the biological relevance of candidate genes.

- Investigate the role of infectious and non-infectious agents as environmental triggers of rheumatic diseases.

- Explore systems biology approaches that investigate the interrelationships between muscle, skin, and cartilage in the integrity and function of joints.

- Explore the generation and maintenance of autoinflammatory and autoimmune mechanisms that damage the joints and other tissues in arthritis.

3A-3) New Discoveries for Diagnosis and Treatment

New genetic, genomic, and proteomic technologies, such as those that allow analysis of the activity of many genes simultaneously and those that uncover protein patterns that predict disease, will help investigators develop new methods to detect the onset and follow the progression of rheumatic diseases. New bioinformatics methods for analysis of genomic and proteomic data will help to identify genes that cause an individual to be susceptible or resistant to arthritis and related diseases and will aid in the discovery of molecular pathways involved in disease onset, progression, and new treatment strategies. Highlights of promising areas of research include:

a. Disease characterization, disease-activity and clinical-outcome measures.

The development of new therapies for systemic autoimmune diseases such as systemic lupus erythematosus has been hampered by the lack of sufficiently reliable measures of disease activity or severity. There is a need for improved measures of disease activity and better techniques for evaluating disease outcomes. The recent NIH Roadmap initiative on Patient-Reported Outcomes Measurement Information System (PROMIS) represents an important step forward in developing and using new methodologies (e.g., computer assisted testing, item response theory) for capturing self-reported outcomes. Highlights of areas of interest include:

- Define disease heterogeneity at the molecular level (e.g., via genotyping or microarrays).

- Develop methods to predict disease pre-clinically using combinations of genetic predisposition, autoantibodies, and other phenotypes (biochemical, mRNA profile, etc.).

- Identify reliable predictors (biomarkers) of rheumatic diseases in children and adults.

- Establish better means to quantify the severity and measure progression of single organ involvement in rheumatic diseases (renal, central nervous system, pulmonary, cardiovascular, and skin) in order to better determine the efficacy of therapeutic interventions.

- Develop pediatric-specific as well as disease-specific tools to measure the activity, severity, and change/response to therapy.

- Encourage studies performed in effectiveness settings and/or in practice-based research networks, to be certain that the treatments that are efficacious in the artificial environment of a clinical trial are also effective in clinical practice.

- Promote research on physical medicine and rehabilitative strategies for reducing impairments, functional limitations and disability.

b. Biological surrogate markers for disease activity

Clinical trials in HIV have been advanced through the identification of agreed-upon surrogate markers of disease activity and progression, such as CD4 count and viral load. Analogous biomarkers are generally not available for systemic autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and scleroderma) and for other forms of inflammatory arthritis. Research to identify and validate markers that reflect clinical disease activity or progression would greatly facilitate development of more effective treatments. These include novel assays for monitoring disease activity, predicting outcome, and predicting disease development. Highlights of areas of interest include:

- Develop and apply new technologies for the discovery of biomarkers of disease onset, progression, and response to therapy.

- Move promising biomarkers from the bench to the clinic using state-of-the-art statistical, analytical, and computational methods.

- Develop new, non-invasive imaging modalities to diagnose and monitor disease activity.

- Link studies of novel therapeutic agents in different rheumatic diseases with mechanistic studies that identify useful biomarkers.

- Encourage basic exploratory studies to identify lead candidate biomarkers.

- Focus on individual organ systems to find better ways of measuring outcomes and validate interventions.

c. New imaging technologies

Advances in cell imaging have vastly changed our ability to appreciate cell trafficking to intracellular signaling to the fine structure of macromolecules. Imaging improves our understanding of cell-cell interactions in lymph nodes, dynamic alternations in the architecture of "immune synapse," and intracellular signaling and transcriptional control. Recently, biosensors have been described that dynamically image macromolecular signaling complexes. These evolving technologies have the potential to be clinically applicable. The ability to image end organ disease early in the course of illness will become increasingly important as therapy improves.

- Promote exploratory and more focused clinical research on new imaging technology for rheumatic disease, e.g., for functional studies, non-invasive imaging, disease prognosis, and following disease course.

- Identify markers for stem cell populations, transient populations, and progenitors useful for *in vitro* and *in vivo* assay.

d. New therapeutics

Advances in immunology, molecular biology, and genetics are resulting in an emerging complement of therapies that needs to be tested in both pre-clinical and clinical trials of rheumatic diseases. Opportunities include identifying therapeutic targets, understanding mechanisms of action of new drugs, and moving toward clinical trials in an organized manner. For example, the study of a cohort of patients with the same disease could provide an understanding of disease outcomes, establish a registry and tissue repository for translational studies, initiate prospective cohort studies, and provide a population for comparison of therapeutic interventions. Specifically, the following areas are identified:

- Revisit the current recommendation for treatment of lupus nephritis.

- Identify new approaches to the treatment of rheumatoid arthritis and spondyloarthropathies (e.g., using disease-modifying agents and/or the new biologics).

- Explore immunosuppressive agents in various inflammatory rheumatic disorders.

- Identify innovative treatment strategies for fibromyalgia.

- Establish mechanisms for multi-center trials for orphan diseases.

- Research the use of new biomaterials particularly for joint replacement with a focus on joints other than the knee or hip.

- Elucidate the long-term effects of new biologic agents for rheumatic diseases, perhaps in collaboration with the Food and Drug Administration and other Federal agencies.

- Expand translational research to phase I (and just pre-phase I) clinical applications.

- Develop small-molecule biologic response modifiers, and extend some of the advances in this area from other fields, such as oncology, to rheumatology.

- Promote improved understanding of common mechanisms of diseases to develop “common therapies.”

- Investigate the mechanisms underlying the therapeutic effects of anti-cytokine therapies. Methods should be developed to monitor the effect of therapy, optimize dosing, time the intervention to disease state, and target responsive patient populations.

- Pursue a better understanding of the epidemiology and disease manifestations for rheumatic diseases such as juvenile arthritis, lupus, and juvenile dermatomyositis, so that interventional trials can be designed.

3A-4) Prevention, Risk Factors and Outcomes Research

Despite some success in identifying risk factors for lupus and rheumatoid arthritis, population studies suggest that other still unidentified factors also influence the incidence of rheumatic diseases. A combination of factors such as a variation in a gene, together with infections, drug exposures, or dietary

habits, could predispose an individual to develop arthritis or a related disease. There is a need to identify new risk factors and develop technological approaches to evaluate them in order to predict disease susceptibility more reliably.

Highlights of areas of interest include:

- Evaluate the ability of markers of early autoimmune responses to identify at risk populations for rheumatoid arthritis, lupus and other rheumatic diseases.

- Evaluate the usefulness of screening tests for early assessment of at risk populations for rheumatoid arthritis, osteoarthritis and lupus.

- Develop a risk factor profile (using genomic technology) for disease subsets with higher risk for severe or rapidly progressing diseases for rheumatoid arthritis and other rheumatic diseases.

- Evaluate the relationships between gender and autoimmunity from the epidemiology perspective – risk factors in human populations.

- Assess the association between dietary factors such as omega-3 fatty acid intake, and antioxidants and rheumatoid arthritis and perhaps lupus severity, and risk of incident disease.

- Evaluate the association between lupus and environmental exposures in case-control studies.

- Study gene-environment interactions between genes that control detoxification of environmental toxins, and silica or solvent exposures.

- Study genotype-exposure interactions on risk of rheumatoid arthritis and lupus.

- Study the mechanisms of cardiovascular complications of rheumatic disease and design interventions to halt progression of cardiovascular disease. Study the effect of new rheumatoid arthritis or lupus treatments on early atherosclerosis and the effect of statins.

- Develop multiple outcome instruments (as in lupus) that can be mapped statistically based on item response theory.

- Continue research on the biological and biopsychosocial factors that contribute to health disparities in rheumatic diseases.

3B) CARTILAGE AND CONNECTIVE TISSUE BIOLOGY AND DISEASES

Highlights of research needs and opportunities include:

3B-1) Genetics of Cartilage and Connective Tissue Diseases

Many aspects of joint structure and physiology are strongly influenced by heredity. However, genetic influences on the development of joint disease are complex, reflecting the contributions of many different genes. Resolving the role of each of these complex genetic factors is a major challenge. Several recent studies have contributed to understanding the factors-- including obesity, age, injury to menisci or cruciate ligaments, repetitive trauma to the joints, congenital malformations, presence of calcium crystals in joints, and undefined genetic factors-- that predispose individuals to developing joint diseases such as osteoarthritis. Taken together, several lines of evidence suggest that human genetic variation is a significant determinant of cartilage and connective tissue degeneration. It has been estimated that 39-65% of the osteoarthritis variance is attributable to genetic factors; however, the number of genes involved could not be determined. For all disease studies, consistent clinical/radiological measures of prevalence, severity, and rate of progression are needed as well as patient information regarding non-genetic risk factors.

Some broad areas of recommended research directions include:

- Exploit newly developed resources that reveal the details of genetic variation in human populations. Public resources such as the Haplotype Map are expected to make possible much more powerful analyses of complex genetic influences on the human skeleton. Existing clinical cohorts, such as the Osteoarthritis Initiative, will provide the phenotypic data necessary for large-scale studies. Population-based studies as well as systematic collection of osteoarthritis families will provide important resources in the search for responsible genes.

- Study the mechanisms by which mutated genes produce disease. Identification of disease-related genes may lead to important new strategies to treat or prevent disease.

- Pursue genetic analysis in mice. Common inbred mouse strains represent significant genetic and phenotypic variation. Quantitative trait locus (QTL) analysis shows promise in detecting genes that contribute to cartilage and joint properties.

- Explore the possible role of epigenetic mechanisms in the varying phenotypic expressions of joint degeneration.

3B-2) Molecular and Cellular Biology of Cartilage and Connective Tissues

The biochemical pathways and cellular interactions that influence the physiology of cartilage and connective tissues are complex. There is a continued need for research on the basic biology of articular cartilage, tendons, and ligaments. Cartilage and connective tissue are complex assemblies of extra-cellular proteins and cells. Studies are needed on the structure and function of matrix macromolecules within the context of their complex environment and the changes that take place during development, repair, and disease. Little is known about the normal assembly and maturation of these tissues, the role of mechanical and biochemical effectors, and their interplay in these tissues during normal function, injury, and disease. Multidisciplinary approaches are needed that couple biochemistry, molecular biology, and genetics with engineering to advance this area of research.

Some broad areas of recommended research directions include:

- Identify the features of the articular chondrocyte phenotype that distinguish it from other forms of cartilage using gene expression and other methods.

- Identify the factors that contribute to chondrocyte cell death in physiology and pathology.

- Explore the interactions between cartilage matrix proteins and how mutations in individual cartilage matrix proteins affect chondrocytes and overall tissue function.

- Study the structure and function of fibrocartilage and the regulation of its formation in various tissues.

- Conduct comprehensive gene expression profiling and cDNA sequencing for normal cartilage, tendon, and ligament development. Use expression profiles to develop models of various disease states.

- Study gene regulation of critical regulatory and signaling proteins for cartilage, tendon, and ligament development. Identify factors involved in development of disease and during the healing stages post-injury as potential targets for interventions.

- Explore the structural organization and the effect of mechanical loading on organization of tendons and ligaments. Explore gene expression and regulation of healing, remodeling, and adaptation in these tissues (particularly tendinopathies) and the cellular and molecular signals that link mechanical loading to gene expression.

- Develop design criteria for engineered cartilage, tendons, and ligaments with particular emphasis on the role of stem cells for improved healing of these constructs.

- Explore the developmental biology of the joint and the interactions among various tissues in the joint and how these interactions might inform our understanding of the development of disease states in the joint. It is possible that some of the biological activities that lead to joint degeneration actually originate in the bone, synovium, meniscus, or other tissues of the joint. The use of genetically modified mice and new tools for genetic analysis in both mice and humans may make it possible to detect the role of these other tissues, if any, in joint degeneration. Such molecular details could suggest novel approaches to preventing and treating degenerative joint disease.

3B-3) Research in Heritable Diseases

Over 200 disorders are recognized as being caused by mutations in genes that encode matrix proteins or in genes that ultimately affect the structure of the extracellular matrix. These disorders are collectively termed heritable disorders of connective tissue. There is a wide range of anatomic sites and clinical manifestations that can result from these conditions. Some mutations in genes may give rise to severe abnormalities, while others may produce milder symptoms. Further work is needed to identify cohorts of patients and families with rare disorders and to recognize structure-function relationships in interpreting genetic mutations.

Some broad areas of recommended research directions include:

- Pursue genetic analysis in mice. Common inbred mouse strains represent significant genetic and phenotypic variation. Quantitative trait locus (QTL) analysis shows promise for detection of genes that contribute to cartilage and joint properties and diseases.

- Study the mechanisms through which mutations result in disease and relate these to the assembly of the connective tissue in question.

- Develop and characterize human and animal cell culture models and genetically engineered animal models for these diseases that could be accessed by the biomedical community.

- Conduct natural history clinical studies in these disorders to better characterize the clinical manifestations and variations in the human population. Establish clinical databases that include molecular and biochemical characterization of these cohorts.

3B-4) Mechanisms of Pathogenesis of Osteoarthritis

Osteoarthritis is the most prevalent joint disorder. However, relatively little is known regarding the etiology, pathogenesis, and progression of osteoarthritis. The disease process not only affects the articular cartilage and causes it to degenerate, but also involves the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles. The common pathway leading to osteoarthritis involves excess damage to the joint tissues, whether the damage is caused by a mutation, inherited, developmental or posttraumatic joint instability, failure of the neuromuscular system to protect against repetitive loading, or metabolic events leading to joint remodeling. Efforts are needed to develop interdisciplinary basic research to investigate the cellular and biomechanical factors that cause joint damage to progress to osteoarthritis.

Some broad areas of recommended research directions include:

- Investigate further the biomechanical and biochemical factors that influence the initiation of the joint changes associated with osteoarthritis.

- Determine the relationship of the inflammatory process and calcium phosphate crystal deposition to the pathogenesis and progression of osteoarthritis.

- Elucidate the role of changes in the bone and other tissues of the joint in the pathogenesis of osteoarthritis.

- Study the role of cellular aging on the onset and progression of osteoarthritis.

- Evaluate the biomechanical and possible biochemical impact of obesity on the development of osteoarthritis in both children and adults. Examine the possible role of advanced glycation end products in joint degradation in obese patients with diabetes.

- Develop new, well-characterized animal models for the study of osteoarthritis.

3B-5) Imaging and Biomarkers in Cartilage and Connective Tissues Research

There has been a tremendous expansion of musculoskeletal imaging methodologies over the past 10 years. New modalities, novel uses of established techniques, and improvements in existing modalities have resulted in increased clinical information about joint structural changes during pathology. Many questions remain with regard to the interpretation and use of these technologies and application of them to diagnosis and monitoring of diseases. A massive number of clinical images will be generated as part of the Osteoarthritis Initiative with X-ray and magnetic resonance methodologies. The use of this and other resources will be of great value in the validation and standardization of such methodologies for wide spread clinical application.

Some broad areas of recommended research directions include:

- Develop and validate new approaches to the imaging of the joint in general, and cartilage in particular.

- Improve links between engineering, physics, mathematics, and imaging groups to facilitate development of measurement tools to identify earlier indicators of joint disease before permanent damage is done to the joint. Techniques such as magnetic resonance imaging (MRI) and optical computed tomography have the potential to resolve details of cartilage and other joint structures well beyond the power of conventional X-rays. The application of these techniques and other novel methods can advance both research efforts in animals and the non-invasive assessment of disease in patients.

The chronic diseases that form the core of the mission of NIAMS often have a very long and variable clinical course. Identifying novel therapies to prevent or delay joint destruction is a common goal for the NIH, the Food and Drug Administration, and the pharmaceutical industry. Therapies to prevent, delay, or repair joint breakdown have not been tested, despite major advances in understanding of the disease, in large part because of the inability to accurately measure disease progression and response to candidate therapies. Efforts are encouraged to further the discovery and validation of biomarkers. Some broad areas of recommended research directions include:

- Develop standard methodologies for evaluation of changes in human joint structure-- including synovium, cartilage, bone, ligaments,

tendons, and meniscus-- associated with aging. Differentiate these changes from those associated with symptomatic joint diseases such as osteoarthritis.

- Develop and validate standardized, sensitive assays for disease-specific markers in tissue specimens or body fluids that enhance diagnosis and enable monitoring and efficacy determination of surgical or pharmaceutical treatments.

3B-6) Drug Therapies and Clinical Trials for Cartilage and Connective Tissue Diseases

The percentage of Americans over 65 years of age is the fastest growing segment of the population, and is expected to reach 68 million people by the year 2010. Osteoarthritis will affect at least 70% of this population. Despite its prevalence, very few, if any, disease-modifying agents exist for the treatment of osteoarthritis or other joint diseases.

Some broad areas of recommended research directions follow:

- Investigate novel agents and approaches to decreasing the disability and pain related to cartilage and connective tissue diseases. Innovative strategies should be pursued to encourage and support approaches to treatment of disease. Currently small scale clinical trials in osteoarthritis are investigating the effects of weight loss and exercise, stability training, vitamin D and natural substances from foods.

- Investigate novel agents and approaches that would lead to the prevention or reversal of structural modifications of diseased joints. Identification of novel targets for disease modification and development of modifying agents are critical needs for moving this area of research forward. Current potential disease-modifying agents being investigated include doxycycline and glucosamine/chondroitin sulfate.

3B-7) Gene Therapies for Cartilage and Connective Tissue Diseases

A number of cartilage and connective tissue diseases are due to mutations in a single gene, either inactivating the gene or producing an aberrant protein product. Knowledge of the mutant gene makes possible gene-based approaches to therapy. In addition, intra-articular injections of viral vectors expressing various cytokine inhibitors, such as interleukin-1 receptor antagonist, have been shown to reduce cartilage breakdown in animal models of inflammatory arthritis. Such therapeutic approaches show promise for local

delivery of agents to joints as part of a broader therapeutic approach to osteoarthritis.

Some broad areas of recommended research directions include:

- Develop and test methods for the targeted inactivation of genes in connective tissue cells from various lineages. Promising approaches include targeted insertion of viral vectors and introduction of small interfering RNAs.

- Develop and test methods for the recovery, genetic modification and re-introduction of cells in the marrow stromal/chondrocyte lineage.

- Investigate possible gene therapy approaches for treatment and prevention of early osteoarthritis and other disorders of connective tissues.

3B-8) Clinical and Outcomes Research

Clinical research, including tests of outcomes in actual practice, is essential to ensure that research advances are translated into public health benefits. Diseases at the core of the NIAMS mission are complex and often develop slowly over time, complicated by the aging process. The development of standardized outcomes and application of these in clinical studies are critical to a clear understanding of the onset and progression of cartilage and connective tissue diseases such as osteoarthritis. The development of appropriate therapies and biomarkers requires a clear understanding of the risk factors and structural components that are associated with well-phenotyped disease.

In many cases, therapies to prevent, delay, or repair joint destruction cannot be easily tested due to our inability to accurately measure disease progression and response to these interventions. There are significant needs for well-conducted clinical research to apply and validate outcome measures. The NIAMS and other NIH Institutes and Centers have partnered with the pharmaceutical industry to establish a research resource, the Osteoarthritis Initiative, to aid in the discovery and validation of disease risk factors, genetic, imaging, and biochemical markers, and improved outcome measures for osteoarthritis. This research resource will be available for use by the public in 2006.

Some broad areas of recommended research directions include:

- Identify, develop, and validate improved outcomes for assessment of onset and progression of cartilage and connective tissue diseases.

While the Osteoarthritis Initiative database will provide a pivotal resource for discoveries and validations, it is important to have other investigator-initiated research in these areas to develop improved outcome measures to be tested. Currently, efforts are being made with regard to the development of MRI surrogates for change in disease status and for the development of computer adaptive testing methods to be used in osteoarthritis clinical trials.

- Study the role of biomechanical and biochemical factors in the initiation and progression of joint changes in clinical populations.

- Develop collaborative research teams with bioengineers, kinesiologists, rheumatologists, orthopaedic surgeons, physiatrists and imagers to improve our understanding of the interactions between joint structures, alignment, and gait. Such collaborations could lead to the development of multidisciplinary and multi-systems approaches to treatment and prevention of disease.

3B-9) Joint Disease Prevention

The cartilage loss that leads to joint degeneration is generally slow and progressive with age. Understanding the factors that determine whether or not disease develops is critical for developing appropriate preventive strategies and therapies for those most in need.

Some broad areas of recommended research directions include:

- Identify and stratify risk factors for osteoarthritis development in individuals and populations, such as body weight, previous joint injury, family history, diet, physical activity, coincident pathology of other tissues and organs, and medication use.

- Modify existing strategies and develop new strategies, including preventative and rehabilitative approaches, to reduce the risk of disability and functional limitation associated with the onset and progression of osteoarthritis.

- Determine the impact of changes in modifiable risk factors on onset and progression of osteoarthritis.

- Explore the use of rehabilitation to reduce risk for impairment due to osteoarthritis progression.

3C) BONE BIOLOGY AND BONE DISEASES RESEARCH

NIAMS is committed to supporting a balanced range of basic, translational and clinical research projects across the full spectrum of musculoskeletal disorders. Among other areas, this includes a broad program of research to better understand the genetic and cellular mechanisms involved in the build-up and break down of bone; work to develop and validate new imaging approaches for bone; and efforts to investigate novel drug and gene therapies for musculoskeletal diseases.

Highlights of research needs and opportunities include:

3C-1) Developmental Biology of Bone

The shaping and growth of bones during infancy and childhood may be an important factor in adult skeletal health. In addition, such processes as fracture repair and joint degeneration may have important parallels with developmental events. Further, the mechanisms of early skeletal growth may yield tools for the replacement of damaged tissues later in life.

Some broad areas of recommended research directions include:

- Study the mechanisms underlying the condensation of embryonic skeletal elements, the progression of chondrocytes through the hypertrophic pathway, the mineralization of growth plate cartilage, and the replacement of cartilage with bone.

- Explore the molecular and cellular basis of genetic disorders that affect skeletal development, including chondrodysplasias.

3C-2) Genetics of Bone Physiology

Many aspects of skeletal physiology are strongly influenced by heredity. However, genetic influences on the skeleton are complex, reflecting the contributions of many different genes. Resolving these complex genetic factors is a major challenge.

Some broad areas of recommended research directions include:

- Pursue genetic analysis in mice. Common inbred mouse strains represent significant genetic and phenotypic variation. Quantitative trait locus (QTL) analysis shows promise in detecting genes that contribute to skeletal properties.

- Exploit newly developed resources that reveal the details of genetic variation in human populations. Public resources such as the Haplotype Map are expected to make possible much more powerful analyses of complex genetic influences on the human skeleton. Existing clinical cohorts may provide the phenotypic data necessary for large-scale studies.

3C-3) Molecular and Cellular Biology of Bone Biology and Bone Diseases

The biochemical pathways and cellular interactions that influence skeletal physiology are complex. Some of these pathways are intrinsic to bone itself, but others involve other tissues and organ systems. In addition, the skeleton is exquisitely sensitive to the environment, especially to mechanical factors.

Some broad areas of recommended research directions follow:

- Identify the molecular and cellular mechanisms underlying the pathology of bone diseases such as Paget's disease of bone, osteogenesis imperfecta, and osteopetrosis.

- Identify the mechanisms underlying the response of bone to mechanical loading. The skeleton responds to the mechanical loads of gravity and muscular contraction by changes in both bone formation and bone resorption. Understanding how bone cells respond to mechanical stimuli and communicate with other bone cells may lead to new ways of controlling bone remodeling in many different situations. Osteocyte networks are a particular target of research directed to understanding the transmission of the load signal to bone tissue.

- Explore the mechanisms of mineralization in bone. The mineralization of bone is critical to its mechanical properties, including its resistance to fracture. There is also evidence that pathological mineralization in other tissues, such as joints and blood vessels, occurs by processes that parallel the mineralization of bone. Little is known about the mechanisms that make possible the controlled, consistent mineralization of bone, while sparing other tissues from this potentially dangerous process.

- Investigate bone malignancies particularly the basic mechanisms of bone tumor cell interactions either as skeletal complications of malignancy or in primary bone tumors. This area is one of partnership with the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases.

- Explore the interactions between bone and the hematopoietic and immune systems. Many bones are partially hollow and filled with marrow, a complex mixture of cells with many essential functions. The marrow produces the cells of the blood, in a process called hematopoiesis. Some of these cells carry oxygen to the tissues and mediate the clotting of blood at sites of injury. Others, the cells of the immune system, defend the body against infection. It is increasingly evident that cells originating in the marrow, especially those of the immune system have the potential to influence bone cells in important ways. Understanding bone-hematopoietic-immune interactions is likely to lead to new insights into disease processes and to identify new targets for therapeutic applications.

- Investigate the linkage between bone and fat metabolism. Recent observations suggest that molecules known to influence the development of fat tissue, which is made up of cells called adipocytes, can have important effects on bone cells. In part, this may reflect the fact that fat-storing adipocytes and bone-forming osteoblasts arise from the same type of progenitor cell. There are also potentially significant parallels between bone loss and the development of cardiovascular disease. Inflammation, which is part of the immune system's response to injury and infection, seems to have a role in both bone loss and cardiovascular disease. The importance of fat metabolism in the development of cardiovascular disease is well recognized, and there are a number of well-characterized drugs that target fat metabolism. Thus, it seems likely that understanding the interplay of bone and fat metabolism would have significant health implications.

- Study the interaction between bone cells and the vascular system. Bone is richly supplied with blood vessels, and the growth of new blood vessels is a critical aspect of bone growth, repair, and remodeling. There may be parallels between bone formation and the vascular calcification that often occurs in cardiovascular disease. Understanding the interactions between bone cells and vascular cells could reveal new therapeutic targets with broad application.

- Identify cell-matrix interactions in bone growth and remodeling. Bone itself is an extracellular matrix -- a complex mixture of proteins and other components produced by osteoblasts. Both osteoblasts and osteoclasts function in close association with the bone matrix. This association is mediated by specific interactions between proteins at the cell surface and components of the matrix. A growing body of evidence suggests that these cell-matrix interactions can have important functional consequences for bone growth and remodeling. Understanding the nature and significance of cell-matrix interactions

may reveal molecular pathways that could be targeted in developing therapies for both bone loss and the inappropriate mineralization of soft tissues. Cell-matrix interactions are also likely to be crucial for using bone-forming cells in tissue engineering applications.

- Explore the influence of the nervous system on bone. Like blood vessels, nerves thread throughout bones, carrying chemical and electrical messages to and from the brain. Recently, evidence has begun to accumulate suggesting that the nervous system can have significant influence on the balance between bone formation and bone resorption. Understanding this communication between bone and nervous system could lead to new therapies to prevent or reverse bone loss. It could also reveal previously unrecognized side effects of drugs already in wide use for the treatment of high blood pressure, seizures, and depression.

- Explore the contribution of bone to degenerative joint disease. In joints such as the knee and hip, the surfaces that normally glide smoothly past one another are made of cartilage. In degenerative joint disease, such as osteoarthritis, this cartilage surface is damaged and degraded, leading to pain and restricted mobility, often necessitating total joint replacement surgery. Because the cartilage surface in joints is thin and supported by underlying bone, it is possible that some of the biological activities that lead to joint degeneration actually originate in the bone. The use of genetically modified mice and new tools for genetic analysis in both mice and humans may make it possible to detect the role of bone, if any, in joint degeneration. If this role is significant, its molecular details could suggest novel approaches to preventing and treating degenerative joint disease.

3C-4) Imaging in Bone Diseases Research

- Develop and validate new approaches to the imaging of the skeleton. Techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have the potential to resolve details of bone well beyond the power of conventional X-rays. These techniques can advance both research efforts in animals and the non-invasive estimation of fracture risk in patients.

3C-5) Drug Therapies and Biologic Agents for Bone Diseases

The key processes in bone remodeling are the formation of new bone and the breakdown, or resorption, of old or damaged bone. The processes of bone formation and resorption are balanced in a healthy adult skeleton. An excess

of resorption over formation results in bone loss, which can lead to osteoporosis and increased risk of fracture. Thus, potentially important therapeutic agents may either inhibit bone resorption or stimulate bone formation.

Some broad areas of recommended research directions include:

- Investigate novel agents and approaches to decreasing the burden of bone disease and fractures. Initiatives like the Pilot and Feasibility Trials in Osteoporosis have targeted innovative strategies that would not be supported by the private sector. Currently small trials are investigating the effect of phytoestrogens, a nitric oxide donor, electromagnetic stimulation and a novel regimen of an approved drug.

- Identify anabolic mechanisms in bone. Anabolic processes are those that form new tissue. Net formation of new bone, which can occur only when bone formation exceeds bone resorption, is critical for therapy in a variety of clinical situations, including post-menopausal osteoporosis. At present, few means are known to induce new bone formation, either at specific sites or throughout the skeleton. Identifying and understanding the processes that induce and control new bone formation are expected to lead to important new therapeutic applications.

3C-6) Gene Therapies for Bone Diseases

A number of bone diseases, such as osteogenesis imperfecta and osteopetrosis, are due to mutations in a single gene, either inactivating the gene or producing an aberrant protein product. Knowledge of the mutant gene makes possible gene-based approaches to therapy.

Some broad areas of recommended research directions include:

- Develop and test methods for the targeted inactivation of genes in skeletal cell lineages. Promising approaches include targeted insertion of viral vectors and introduction of small interfering RNAs.

- Develop and test methods for the recovery, genetic modification and re-introduction of cells in the marrow stromal/osteoblast and macrophage/osteoclast lineages.

3C-7) Clinical and Outcomes Research

Clinical research, including tests of outcomes in actual practice, is essential to ensure that research advances are translated into public health benefits.

Some broad areas of recommended research directions include:

- Conduct long-term prospective studies to ascertain fracture risk in the general population. NIAMS supports several longstanding prospective cohort studies (The Study of Osteoporotic Fracture, Mr. OS (the study of osteoporosis and other age-related diseases in men), the Framingham Study, and the Rochester Epidemiology Project) that continue to investigate and illuminate the most significant risk factors for fractures in older men and women. These cohorts and several others are also contributing the validation of new surrogate markers, both biochemical and imaging. In addition, the bone phenotypes collected are serving as a basis to test genetic susceptibilities as important genetic loci are determined from studies in mice.

- Study the role of nutrition in bone health. The importance of calcium and vitamin D in bone health is well known. The improvement of nutritional status in deficient populations continues to be a focus of the clinical bone research portfolio. Vitamin D has recently been associated with a reduction in falls, so deficiencies in this vitamin could contribute to fractures through falls as well as low bone density. The results from large intervention studies like the Women's Health Initiative Calcium/Vitamin D Trial announced in February 2006 will guide future plans in this area. The scope of nutritional approaches to bone health has broadened with the recognition that an overall eating pattern that has adequate protein and an appropriate balance of other vitamins and minerals can be the key to optimizing the skeleton in youth and retaining bone in old age. The potential for manipulating the dietary acid/base balance through dietary means has been suggested in both Bone Health and Osteoporosis: A Report of the Surgeon General (2004) and the Dietary Guidelines for Americans.

- Study the effect of exercise, physical activity and specific rehabilitative strategies on the improvement in bone mass, the prevention of fractures, and the recovery from fracture.

3C-8) Bone Disease Prevention

The bone loss that can lead to osteoporosis and fracture is slow and progresses with age. Understanding the factors that determine whether an individual is at risk for fracture could help to target preventive therapies to those most in need.

Some broad areas of recommended research directions include:

- Define bone quality and develop the methodology for measuring it. Bone mineral density assessment by Dual Energy X-ray absorptiometry remains a great asset and clinical tool to identify a population at highest risk of osteoporotic fracture. While reduced bone density is important in contributing to and predicting an increased risk of fracture, low bone density alone is not always a sufficient explanation for osteoporotic fractures and lack of change in bone density does not always indicate inadequate therapeutic effect of treatment. Other qualities of bone that may impact on strength such as geometry, macro and micro-structural organization, distribution of material within bone, biochemical composition, and the burden of unrepaired microdamage of bone are currently under study. NIAMS enhanced the effort in the area of bone quality in 2002 by issuing a Request for Applications aimed at elucidating mechanisms and measurement of bone fragility and to develop new strategies and methodologies to identify those at risk for osteoporosis-related fractures and in need of therapeutic intervention to prevent such fractures. These included both basic and clinically oriented approaches. A meeting on bone quality co-sponsored with the American Society for Bone and Mineral Research (ASBMR) in May 2005 was designed to highlight and discuss all of the current innovative approaches and to drive the next generation of research in this area.

- Identify environmental risk factors for bone loss and fracture, such as diet, physical activity, coincident pathology of other tissues and organs, and medication use.

3D) ORTHOPAEDICS

Highlights of research needs and opportunities include:

3D-1) Biomaterials and Implant Science

Recent advances in bioengineering and biomaterials have had substantial impact in many areas of musculoskeletal structure and function. Some of these include: joint replacement; fracture management and fixation; spinal and joint stabilization; internal and external fixation devices; and application of devices to musculoskeletal tissues using robotics and computer-controlled navigation systems. Total hip and knee replacements in particular, have been shown to be effective tools to treat end-stage arthritis that has not responded to non-operative treatment. Both result in improved patient function and quality of life. The following are some of the important research needs and opportunities in this area:

- Continue to develop and validate imaging technologies to better evaluate prosthesis fixation, remodeling and wear.

- Investigate the factors governing implant wear and the host tissue response to wear debris.

- Elucidate the role of the innate and acquired immune system in the pathogenesis of implant failure.

- Assess the impact of small incision, minimally invasive surgical approaches, and robotic surgery on functional outcomes, complications, and revision rates.

- Develop and validate pre- and post-operative rehabilitation strategies, especially for hip and knee replacement.

3D-2) Regenerative Medicine

Regenerative medicine is an important area in orthopaedics, and information on NIAMS needs and opportunities in this area can be found in the Cross-Cutting Areas at the beginning of this document.

3D-3) Soft Tissue Injuries

Musculoskeletal soft tissues include ligaments, tendons, muscles, nerves, cartilage, and the intervertebral disc. These soft tissues are vulnerable to injury and damage as the result of overuse; recreational, sports and occupational activities; and other types of trauma. These strains, sprains, contusions, tendinopathies, bursitis, lacerations, rupture, crushing, and compression are common, costly, and potentially disabling. The following are some of the important research needs and opportunities in this area:

- Develop strategies to block the formation of tendon adhesions.

- Increase understanding of the causes of peripheral nerve compression, develop better animal models, and develop alternatives to surgical treatment.

- Develop improved methods of peripheral nerve repair and regeneration.

- Apply physical medicine and rehabilitative strategies to soft tissue injuries to restore maximal function.

3D-4) Fractures and Skeletal Trauma

Accidents are the greatest cause of death and disability in young people. Of victims of nonfatal accidents with multiple injuries, more than 70% sustain a skeletal injury requiring treatment. In addition to health care costs, these injuries cause billions of dollars in terms of lost employment and sometimes lifetime disability. In addition, it is estimated that 50% of women over the age of 50 years and 33% of men over age 70 will sustain a fracture secondary to osteoporosis. These injuries will become more prevalent as the population ages. The prevention and treatment of fractures and multiply injured patients is the highest priority in musculoskeletal care. After injury prevention, methods to reduce complications, disability, and mortality are paramount. Further refinement of operative and non-operative techniques and rehabilitation will improve outcomes, facilitate return to work, and provide for a better quality of life. The following are highlights of some of the important research needs and opportunities in this area:

- Development of enhanced strategies to recognize and treat combined injuries, especially as they relate to: timing and type of surgery in multiple trauma patients; head injury; chest injury; and shock.

- Improvement of the management of specific skeletal injuries, especially related to minimally invasive surgery, the mangled extremity, compartment syndromes, and fractures in the elderly.

- Further elucidation of the outcomes and cost-effectiveness of treatments for specific fractures/injuries.

3D-5) Childhood Musculoskeletal Conditions

Childhood musculoskeletal conditions involve problems with the muscles and soft tissues, bones, joints, spine, and limbs. They are frequently classified into: genetic and congenital malformations present at birth; developmental problems occurring spontaneously during growth; neuromuscular diseases; trauma from accidents, abuse, and injury; and tumors and infections in bones and connective tissues. The cost of these conditions is enormous. Although some conditions can be treated with a full restoration to active life, others can result in early death or progressive problems into adulthood. Some present lifelong challenges to the individual, family, and society. Trauma is the leading cause of death after the first year of life; it exceeds all other causes of childhood death combined. Prevention of childhood injury is a public health imperative. The following are some of the important research needs and opportunities in this area:

- Investigate the developmental biology of the musculoskeletal system with emphasis on bone and joint development and mechanism of regeneration.

- Develop more physiologic interventions for the correction of skeletal deformities and neuromuscular conditions, including cerebral palsy and muscular dystrophies.

- Study the musculoskeletal implications and complications of rheumatic diseases in children including growth delay, osteoporosis and avascular necrosis.

- Design and conduct clinical studies to determine optimal therapeutic approaches to these conditions as new treatments are developed.

3D-6) Sports and Fitness

Fitness is a term that encompasses an array of health-related activities that lead to optimal body size, shape and function. Fitness is associated with good health and a sense of well-being. These goals can be achieved through daily activities that include a minimum of 30 minutes of aerobic and resistance exercise. The exercise requirements vary with age and individual comorbidities. Numerous studies have shown the beneficial effects of exercise in disease prevention. One of the problematic effects of exercise is injury. The following are some of the important research needs and opportunities to identify optimal exercise strategies prevent injury, and when it occurs, to facilitate recovery from musculoskeletal injury:

- Develop a better understanding of the particular fitness requirements for different genders, for different age groups, and for individuals with different physical disabilities.

- Study the pathomechanics of joint injury focusing on prevention and the development of more effective protective devices for particular sports and jobs, where risks of physical impairment exist.

- Develop a better understanding of gender differences in ultra-high performance sports that can lead to focused programs of prevention of disorders associated with these athletes.

3D-7) Spinal Disorders

Spinal disorders include cervical, thoracic and lumbar spine pain, nerve pain, sprains, injuries/fractures, degenerative disc disease and arthritis, spinal

stenosis, tumors, and deformities. Many of these disorders are common, costly and potentially disabling. Low back pain affects millions of people around the world and has an enormous socio-economic impact. In industry, it is a frequent cause of disability, generating an enormous number of working days lost per year. Although low back pain constitutes an important public health issue, little is known about its pathogenesis. The structure of the spine is so complex that the causes of low back pain are almost certainly multi-factorial. Moreover, degenerative disc disease is thought to be the major cause of chronic low back pain in western societies.

The following are highlights of some of the important research needs and opportunities in this area:

- Improve understanding of the basic biological processes associated with spinal disorders and their associated pain syndromes.

- Explore new treatment methods and technologies for degenerative disc disease, including the use of artificial disc and nucleus, and the use of regenerative medicine techniques to reverse the process of disc degeneration.

- Implement clinical studies for specific spinal disorders that are common and costly, and where there is a controversy regarding optimal treatment.

3D-8) Work-Related Injuries

Musculoskeletal injuries related to the workplace are among the most costly health problems facing society today. The economic burden of these musculoskeletal problems is conservatively estimated at between $45 billion and $53 billion annually. The majority of these work-related injuries currently involve the back and upper extremity. The literature recognizes that injury risk arises from many simultaneously contributing factors that include: workplace physical factors, organizational factors, and psychosocial factors. The National Institute of Occupational Safety and Health (NIOSH), of the Centers for Disease Control and prevention, is the Federal Government's focal point for work-related research. The NIAMS is specifically interested in basic science studies that can further elucidate the causes of these injuries in musculoskeletal tissues, and in studies to assess the effectiveness of operative and non-operative treatments for these injuries (whether work-related or not). The section on Soft Tissue Injuries earlier in this document includes related research opportunities.

3D-9) Clinical Research

There continues to be a need for a broad range of patient-oriented research studies in musculoskeletal injuries and disorders. Some of these needs and opportunities have been listed in the preceding sections. Relevant studies should target clinical conditions that are common, costly, and have conflicts regarding what is the most optimal form of treatment. Although strides have been made in delineating general and disease-specific health status measures to assess the effectiveness of treatment, further standardization within the orthopaedic community, and if possible, among all provider groups who engage in "musculoskeletal medicine," could allow for the analysis of outcomes across and within disciplines. If successful, this would allow health care providers to modify their practice, based upon sound scientific studies, in order to do the interventions that are best for the patient and most cost-effective for society.

One goal of clinical research should be to serve as the foundation for "evidence-based medicine." In addition, there continues to be a need to better understand health disparities in the treatment of musculoskeletal injuries and disorders. Suggested areas of study continue to include: assessment of health care utilization in minority populations; economics of health care; and racial differences in preferences for musculoskeletal care. Finally, there continues to be a need to train clinician scientists. The NIAMS will continue to work with our communities to offer appropriate mechanisms to meet this need.

3E) MUSCLE BIOLOGY AND DISEASES RESEARCH

It is a high priority for NIAMS to support a balanced range of basic, translational and clinical research projects in skeletal muscle biology and muscle diseases. We encourage the study of all of the muscular dystrophies, inflammatory myopathies and muscle ion channel diseases as well as muscle disorders such as injury, disuse atrophy and age-related loss of muscle mass. Studies of basic skeletal muscle cell and developmental biology, structural biology, physiology and biomechanics are essential for developing the depth of understanding of muscle biology that is conducive to the germination of pivotal discoveries. There is also a need for increased translational research to develop these discoveries into advances in treatments and improvements in the management of muscle and musculoskeletal diseases and disorders.

Highlights of research needs and opportunities include:

3E-1) Muscle Cell and Developmental Biology

Understanding healthy and diseased muscle states requires basic study of skeletal muscle tissue development and maintenance and investigations into the interaction and function of muscle cells and their subcellular components.

Broad areas of recommended research directions follow:

- Continue to study the cellular events in muscle development including embryonic cell fate determination, progenitor cell migration, cell fusion, and patterning and tissue formation.

- Continue to explore the growth factor and cell adhesion signaling that regulates and coordinates these cellular events.

- Continue to characterize satellite cells and other muscle cell types that contribute to muscle growth, maintenance and regeneration. Explore the extracellular and intracellular signals that regulate their activation, migration, proliferation and differentiation.

- Expand the genomics and proteomics analysis of skeletal muscle states including pre- and postnatal developmental stages, healthy adult, exercised, injured, diseased, atrophied and aged.

- Study the structure and assembly of macromolecular complexes essential for skeletal muscle function and maintenance, including the dystrophin/glycoprotein complex, contractile apparatus and ion channel complexes.

- Characterize the signaling pathways, transcriptional control and gene expression events that regulate hypertrophy and fiber type determination/selection in response to exercise or disease.

3E-2) Muscle Function Research

Improved methods for analyzing muscle biomechanical and metabolic function will advance the detection and diagnosis of muscle diseases and can be used to measure outcomes in clinical trials.

Broad areas of recommended research directions follow:

- Develop or improve non- or minimally-invasive methods to evaluate and quantify muscle strength and performance including functional MRI and other imaging techniques, spectroscopic methods, electromyography, strength testing, etc.

- Conduct natural history studies of muscle function in healthy, aged, exercised, injured and diseased muscle in animal models and human subjects.

- Investigate the molecular and biochemical bases of gender differences in muscle function and response to exercise, diet, age and disease

- Investigate the molecular and biochemical causes of skeletal muscle fatigue and explore approaches to control fatigue.

- Continue to investigate how changes in muscle efficiency are dependent on load, temperature and fatigue.

- Explore the function of muscle as an endocrine organ that influences the activities of other tissues through factors secreted into the bloodstream.

3E-3) Genetics and Pathophysiology of Muscle Diseases and Disorders

There are many diseases that primarily affect skeletal muscle and the genetic basis is known for some, but not all of these diseases. An understanding of how specific gene mutations lead to abnormal phenotypic characteristics of each muscle disease will not only provide insight into disease pathways and physiology of normal muscle and other tissues but will also lead to the development of rational treatment strategies.

Broad areas of recommended research directions follow:

- Characterize the gene defects and molecular consequences associated with muscle diseases. Analyze genotype/phenotype correlations to better understand the functional domains of the gene and to customize treatment or contribute to the determination of prognoses.

- Study the pharmacogenetics of responses to treatment.

- Investigate mechanisms of disease onset and build an understanding of how some muscles are selectively affected by certain diseases, while others are selectively spared.

- Study events in the onset of muscle diseases and identify early biomarkers based on biochemical, imaging or biomechanical parameters.

- Conduct studies on the causes and treatments of muscle pain and the impact of muscle pain on muscle disease patients and on otherwise healthy individuals.

- Continue studies on the cellular and molecular events associated with inflammatory response, muscle scarring and fibrosis during disease progression and in response to injury.

- Continue to investigate the molecular mechanisms of disuse atrophy and explore approaches to block or reduce muscle degeneration. Examine the progression of other muscle diseases in order to determine whether their therapeutic approaches can be used to counter the pathophysiology of atrophy.

- Investigate immune reactions and inflammation in muscle tissue as it relates to myositis, muscular dystrophies, muscle injury and response to strenuous exercise. Investigate the active participation of muscle cells in immune reactions.

3E-4) Muscular Dystrophies

Specific research objectives for the muscular dystrophies have been delineated in the "Action Plan for the Muscular Dystrophies". This document was developed by the Federal Muscular Dystrophy Coordinating Committee (MDCC), with input from experts in the fields of muscular dystrophy pathophysiology, diagnosis, treatment approaches and patient and family care. These documents are available for download at the MDCC website (see link below). NIAMS encourages studies that address these objectives.
http://www.ninds.nih.gov/find_people/groups/mdcc/index_pr.htm

3E-5) Inflammatory Myopathies

There is a need for research specifically focusing on the inflammatory myopathies, including dermatomyositis, polymyositis and inclusion body myositis. Areas of recommended research include:

- Clarification of the cellular and molecular processes by which muscle tissue is damaged and repaired in the inflammatory myopathies.

- Studies that establish and clarify the role of cell-mediated and antibody-mediated immune responses to muscle substances and muscle-related structures.

- Studies aimed at exploring pathogenetic mechanisms involving mitochondrial dysfunction and oxidative stress in skeletal muscle diseases.

- Delineation of the potential role of neurogenic influences in the origin of inflammatory muscle disease.

- Studies that define standard approaches to evaluate disease activity, disease damage, and clinical outcomes.

- Studies that develop improved diagnostic procedures for inflammatory muscle diseases.

- Imaging techniques to improve our understanding of inflammatory muscle disease mechanisms and monitor their treatment.

- Development, use, and sharing of appropriate animal models for inflammatory muscle disease.

- Studies that examine the role of programmed cell death (apoptosis) in the process of muscle fiber degeneration.

3E-6) Drug Therapies and Biologic Agents for Muscle Diseases and Disorders

Despite significant advances in understanding the mechanisms of muscle diseases, current treatment strategies do not take advantage of this knowledge and exhibit limited efficacy.

Broad areas of recommended research directions follow:

- Continue to explore therapies for muscle diseases that are made possible and guided by an understanding of the pathophysiology of these diseases.

- Continue to explore opportunities to enhance or alter the pathways that regulate muscle growth and regeneration for the treatment of diseases and disorders.

- Investigate the mechanisms of drugs currently used in the treatment of muscle diseases in order to develop improved pharmacologic agents with greater efficacy and reduced adverse side effects.

- Explore opportunities to delay or prevent the onset of muscle diseases, in anticipation of a time when screening and early detection is more widespread.

3E-7) Cellular Therapies

The use of isolated cells for muscle tissue regeneration or the delivery of genes offers great potential as therapies for muscle diseases and disorders. However, significant obstacles to the application of these therapies exist, including low efficiency in the survival and integration of grafted cells and the inefficient dispersal of the cells throughout affected muscle tissue. These obstacles may be overcome by identifying appropriate cell types and optimizing conditions for their use.

Broad areas of recommended research directions follow:

- Explore the potential of cells derived from different sources (such as embryos, muscle, bone marrow and other tissues) to regenerate skeletal muscle.

- Characterize cell types with the greatest potential for migration to and regeneration of muscle tissue. Develop efficient methods for purifying, expanding and delivering these cells.

- Study autografting of cells that have been modified to restore the function of mutated genes.

- Investigate the use of signals such as growth factors, extracellular matrix molecules or over-expressed transcription factors to stimulate the engraftment and cell survival and to promote cell proliferation and differentiation into muscle tissue.

3E-8) Molecular Therapies

Molecular therapies offer the possibility of restoring function to a defective gene or compensating for the loss of gene function. These approaches are potentially quite powerful and could lead to significant advances in the treatment of diseases of muscle and other tissues. However, there are many approaches to explore and technical hurdles to overcome.

Broad areas of recommended research directions follow:

- Test promising vectors, therapeutic genes, expression cassettes and local and systemic delivery methods for viral gene therapy.

- Study the immune reaction to gene therapy approaches and investigate ways to readminister the gene for long-term expression.

- Explore methods for editing gene products *in vivo*, such as exon-skipping antisense oligonucleotides and small nuclear RNAs.

- Optimize methods for restoring the expression and function of proteins from mutated genes, such as stop codon read-through.

- Explore opportunities for gene expression upregulation capable of compensating for the function of disrupted genes.

- Evaluate the major organs in inflammatory myopathies in observational and intervention studies that include clinical, immunological and genetic phenotype analysis.

3E-9) Clinical Research

There is a significant need to expand and intensify clinical research on muscle diseases and disorders. In addition to clinical trials, NIAMS also encourages natural history, epidemiologic and behavioral studies, outcomes research and health services research.

Broad areas of recommended research directions follow:

- Expand the number of investigators and further promote the training of investigators engaged in clinical studies of muscle diseases and disorders.

- Promote communication and collaborations among physician-scientists with expertise in muscle health and disease including neurologists, physiatrists, sports medicine researchers, kinesiologists and physical therapists.

- Promote studies of muscle diseases related to quality of life and psychosocial complications.

- Analyze the modern natural history of muscle diseases in relation to patient ethnicity, age, demographics and clinical care.

- Make full use of existing resources for designing and implementing clinical studies, including registries and repositories of patient information, clinical data and samples.

- Develop, validate and promote the use of standardized outcome measures in muscle disease clinical studies.

- Explore additional avenues for the recruitment of patients for clinical studies so that the number of appropriate subjects does not limit the progress of the studies.

- Coordinate activities and develop synergistic interactions among all stake holders in clinical research of muscle diseases including NIH Institutes, NIH-supported researchers, biotechnology and pharmaceutical companies, voluntary health organizations, the Centers for Disease Control and Prevention, the Department of Defense and other federal and private organizations.

3F) SKIN BIOLOGY AND DISEASES RESEARCH

Tremendous needs and opportunities exist in the field of skin diseases research, from work to deepen our understanding of the molecular and developmental biology of skin and its appendages, to new approaches for developing artificial skin, to advances in imaging technologies for diagnosis and tracking of skin disease progression. The NIAMS is committed to pursuing these and other avenues of promising research to improve health outcomes for patients with skin diseases.

Highlights of research needs and opportunities include:

3F-1) Developmental Biology of Skin

The study of embryologic events in the development of skin and its appendages has been greatly facilitated by the understanding of basic signaling molecules and events. Naturally occurring and inbred animal models have been invaluable in this area and will continue to be studied. Transgenic technology has been applied to these studies as well, allowing the molecules of interest to be selectively deleted (knock-out models) or overexpressed (knock-in models) either generally or in selected tissues. The effects of these molecules on skin development can therefore be studied in more detail and more mechanistically.

Some broad areas of recommended research directions include:

- Encourage multisystem basic research in physiology because genes, molecules, hormones, neurotransmitters, and cells all work together in the progression of disease and in therapeutic interventions.

- Continue to examine the finding that the deletion of some apparently key molecules has no effect due to backup or alternative pathways, whereas the deletion of other molecules can be unexpectedly lethal.

- Elucidate the finding that molecules thought to act in one organ system have unexpected effects when deleted or over-expressed in the skin.

3F-2) Molecular Biology of Skin and Its Appendages

The field of molecular biology includes basic studies of the molecules that make up the skin and its cells, such as studies of how these molecules are assembled into the structures that we see under the light and electron microscope, how skin cells interact with one another via cell-to-cell signaling and attachment, how the skin protects itself from the external environment, and how protection can be breached in a controlled manner to apply drugs to treat skin and systemic diseases.

Some broad areas of recommended research directions include:

- Conduct stem cell research in skin as a precursor to gene-therapy approaches.

- Conduct studies of the blood-vessel cells of the skin and angiogenesis.

- Encourage research on junctions, cell motility and cell signaling, and migrations and morphogenesis of keratinocytes.

- Conduct basic studies of skin appendages, including the hair follicle. The hair follicle is interesting in and of itself, but also because it is a model system for cycling cells and structures and developmental and cell-signaling pathways.

- Foster basic wound-healing research, such as research into the control of cell maturation and differentiation that examines changes in the wound-healing process that result in malignancy.

- Evaluate the impact of existing mechanisms to support young basic researchers and explore ways to make clinical skin research compelling to investigators. It is also necessary to support role models and mentors in the field.

3F-3) Percutaneous Penetration and Absorption

A major function of the skin is to prevent water loss from inside the body and the penetration of chemicals from outside the body. It is not completely clear, however, how this barrier function is accomplished.

Some broad areas of recommended research directions include:

- Research how the skin acts as a barrier.

- Develop new treatments for skin diseases as well as topical or skin-based treatments for systemic diseases. In the past, simple patches have been used to deliver the few pharmaceuticals that could structurally penetrate the skin (e.g., scopolamine for motion sickness and nicotine patches). However, we are now on the verge of developing techniques that allow charged molecules, which the skin resists more strongly, to bypass the barrier. Such techniques could open potential new delivery routes to a number of pharmaceuticals.

3F-4) Wound Healing

The inability of chronic wounds to heal is a major health problem in the United States, and the problem will increase in magnitude as the population ages. There have been a number of meetings on this topic, and several mechanisms are being used to stimulate research in the healing of chronic wounds.

Some broad areas of recommended research directions include:

- Study growth factors in normal wound healing.

- Develop more effective wound coverings, including methods to keep the wound moist and the use of artificial bioengineered skin replacements.

- Conduct research on the combined use of growth factors and bioengineered skin with wound coverings that have been genetically manipulated to produce growth factors in a sequence more similar to that of a normal state.

3F-5) Inflammatory and Immune Skin Diseases and the Skin as an Immune Organ

Many autoimmune diseases primarily or exclusively attack the skin as an end organ. Many other skin diseases are inflammatory without involving autoimmunity.

Some broad areas of recommended research directions include:

- Conduct research to improve understanding of the process of autoimmunity in general and of autoimmune skin diseases in particular, including pemphigus, pemphigoid, psoriasis, lupus erythematosus, alopecia areata, vitiligo, vasculitides and others.

- Conduct research using normal-appearing skin from genetically susceptible people to study trigger factors for disease expression and the mechanisms involved in disease development, progression, and involution.

- Research the mechanisms and control of inflammation because control is the key to treating these diseases.

- Improve treatments for skin infections. The response to infection is basically via inflammatory mechanisms, and some infections may trigger autoimmune responses or dysregulated inflammatory responses (psoriasis may be initiated by these mechanisms).

- Study the skin as an active immune organ, focusing particularly on immunocompetent cells that are both resident within skin and trafficking through skin. Such study is important in many diseases, such as HIV and irritant and allergic contact dermatitis (e.g., poison ivy and other kinds of dermatitis, many of which are occupationally related).

- Develop new drugs and devices to treat inflammatory and immunological diseases, as well as other skin diseases.

- Investigate the role of the immune system in the initiation, development, and treatment of skin cancer.

3F-6) Molecular Genetics of Skin Diseases

The field of molecular genetics research has been successful in identifying the genes responsible for single-gene skin diseases, such as the epidermolysis bullosa group of diseases, as well as some of the ichthyoses.

Some broad areas of recommended research directions include:

- Assess and apply existing gene-array and protein-array data and encourage new array studies.

- Conduct genomics and proteomics research that explores the pathophysiology of skin diseases.

- Continue to catalogue specific gene defects and to determine how these defects are translated into the clinical appearance of various diseases. This genotype-phenotype correlation is important not only in understanding and predicting the severity of a disease, but also in opening new avenues to correction of the defects in the disease.

- Expand the use of small interfering RNA technology in gene function studies.

- Attempt to better understand skin disease subpopulations through single nucleotide polymorphisms.

- Continue to search for the genetic basis of diseases, such as vitiligo, psoriasis, alopecia areata, and others, through population-based or family-based molecular genetic studies.

3F-7) Imaging in Skin Diseases Research

The recent development of new imaging technologies and the refinement of existing ones have created the potential to improve not only skin disease diagnosis but also scientists' overall understanding of skin disease progression and pathology.

Some broad areas of recommended research directions include:

- Explore three-dimensional imaging using high-resolution MRI, Raman system, infrared imaging, and other new imaging technologies for use both in medical approaches and in modeling interventions.

- Educate the clinical and research community about imaging techniques and their uses through workshops and small meetings.

3F-8) Technology Research

There have been numerous advances in our basic understanding of the normal structure and function of skin and the abnormalities that result in skin diseases. Often, these approaches are driven by technology. Research in this area should be nurtured.

Some broad areas of recommended research directions include:

- Emphasize technology-driven research because it has the potential to directly affect the health and welfare of the population. Microarray technologies, including gene chips, are merely the newest technologies to be applied to skin disease research.

- Study how mutations lead to aberrant gene expression and abnormal gene products and how these defects result in disease.

3F-9) Drug Therapies and Biologic Agents for Skin Diseases

Translating laboratory research into effective treatments for skin diseases is the ultimate goal of skin research until diseases can be prevented or cured.

Some broad areas of recommended research directions include:

- Consider drug development initiatives that involve collaborations among NIH-supported researchers, industry, academia, research advocacy groups, and other federal agencies, including the Food and Drug Administration.

- Study the pathophysiology of the biologic agents used currently to treat rheumatic and autoimmune conditions to learn more about the implications of these agents for skin disease treatment.

3F-10) Gene Therapies for Skin Diseases or Gene Therapies That Use Skin

Gene therapy continues to be an area of great promise. The skin is unique in its accessibility to gene-therapy approaches, for both skin diseases and other diseases (skin can be a factory for the production of molecules, such as insulin and human growth hormone that are used in the treatment of systemic diseases). One advantage of using skin for gene therapy is that the genetically altered skin can be removed by simple excision if problems develop.

Some broad areas of recommended research include:

- Continue to develop gene therapies for skin diseases using *in vivo* and *ex vivo* approaches.

- Develop new skin-utilizing gene-therapy interventions for systemic diseases. Although several avenues of approach are in the last stages of testing prior to human testing, problems remain that must be solved before such approaches can be widely used.

- Use multiple models of skin disease for gene-therapy studies including rodents, zebra fish and other mammalian and primate models, when appropriate.

3F-11) Regenerative Medicine

The field of regenerative medicine includes the development of artificial skin. Artificial skin was originally created from simple keratinocyte sheets but has evolved into a multi-component material including an artificial dermis. Regenerative medicine-- often focusing on stem cell research-- is a rapidly advancing applied field with potential benefits for skin research, such as the treatment of burn wounds, the treatment of chronic wounds, and gene-therapy interventions. Many of these applied areas of investigation may be supported by the pharmaceutical and biotechnology industries. Some of these areas of investigation are at the cutting edge of basic research, including not only genetic manipulations of the skin but also development of artificial matrices to support the cellular components. Further information on NIAMS needs and opportunities in this field can be found in the Cross-Cutting Areas section at the beginning of this plan.

3F-12) Clinical and Outcomes Research

In dermatology, there is great variability in the therapies and medications that different clinicians use to treat the same disease. Clinical trials and outcomes research provide comparison data for clinicians to make evidence-based decisions. Clinical trials are a costly type of clinical research, however, and they require significant staff and organizational resources. It is therefore crucial to make judicious choices about which trials are pursued with the limited resources available.

Some broad areas of recommended research directions include:

- Continue to expand the base of well-trained and well-supported clinical researchers and clinical trial experts in dermatology via an increased emphasis on epidemiology and clinical trial design in residency as well as in research training programs.

- Evaluate the impact of existing mechanisms to support young clinical investigators and explore new ways to make clinical skin research compelling to investigators. It is also necessary to support role models and mentors in the field and to draw from the related expertise of professionals in schools of public health and elsewhere to supplement those in dermatology.

- Develop new data instruments that better measure disease severity and provide uniform descriptions and data that are comparable across studies. These instruments should include both disease-specific criteria that adequately represent status change and response to intervention, as well as global criteria that address the impact of skin diseases on the individual.

- Assess the usefulness of existing data instruments that measure the burden of skin disease, particularly ones that consider patient and family quality of life and caregiver burden. These burden-of-disease assessment tools can be used to evaluate skin disease interventions.

- Consider important drug-therapy comparison studies and rare disease research that industry is unlikely to undertake.

- Make the data from long-term studies of large cohorts, such as the psoralens with ultraviolet A (PUVA) study, available to researchers so they can compare patients over time.

- Conduct behavioral and psychobiology studies that have the potential to improve understanding of the mechanisms of skin disease.

- Conduct studies on the causes and treatments of itching, which is a significant clinical problem.

3F-13) Skin Disease Prevention and Aging Skin

The population in the United States is aging. The consequences of aging on skin are due not only to chronologic effects but– probably to an even greater extent– to accumulated environmental damage. Much of this damage is caused by ultraviolet (UV) radiation from the sun, and, for those who frequent tanning salons or use tanning beds, from artificial sources as well. Damage is found in the epidermis. This skin layer becomes discolored, dries out (thus changing its resistance to chemical penetration), and can develop skin cancers, precancers, and benign tumors. In the dermis, skin loses adnexal structures (e.g., hair, sebaceous, and sweat glands), thins, and becomes fragile.

Some broad areas of recommended research directions include:

- Develop interventions that reverse, not merely delay, the adverse changes that occur in aging skin.

- Increase prevention research. Because most of the adverse effects due to aging are from ultraviolet (UV) radiation, behavioral modification research and protective behaviors will be necessary to maximize realistic UV avoidance, particularly during the teenage years of life.

- Educate the public about the importance of skin and skin integrity.

4) CONCLUSION

Bones, muscles, joints, and skin are central components of the human body. We now understand better how they develop and function normally, and how they are altered in disease. Recent advances have illuminated the roles of genetics, the environment, diet, and behavior in disease. Perhaps most noteworthy, we are making progress in our efforts to identify those at-risk for developing disease, so we may focus on improved prevention strategies to preserve function and reduce disability and premature mortality. This long-range plan underscores the commitment of the NIAMS to identify and respond to promising scientific opportunities and emerging public health needs across the spectrum of our research portfolio, for the benefit of the American public.