National Institute of
Arthritis and Musculoskeletal
and Skin Diseases

Long-Range Plan
Fiscal Years 2015-2019

Turning Discovery Into Health

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EXECUTIVE SUMMARY

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) advances health through biomedical and behavioral research, as well as through research training. The Institute's research portfolio includes five core mission areas: Arthritis and Rheumatic Diseases, Skin Biology and Diseases, Bone Biology and Diseases, Muscle Biology and Diseases, and Musculoskeletal Biology and Diseases. NIAMS supports research and research training at a variety of levels, ranging from preclinical research with model systems to translational studies to clinical and epidemiological research.

NIAMS invests its taxpayer funds strategically to ensure that creative scientists have the tools they need to make breakthrough discoveries in mission-central areas, as well as in newly defined fields that emerge naturally from the investigative process. NIAMS maximizes return on its investment by encouraging the development and sharing of state-of-the-art resources, as well as by promoting broad dissemination of scientific and health-related knowledge to the Institute's varied stakeholder communities.

The purpose of the NIAMS Long-Range Plan for Fiscal Years (FY) 2015-2019 is to inform the Institute's priority-setting process. The Plan also serves as a platform to facilitate communication between the Institute and its many constituents ─ scientific communities, health care providers, health advocacy organizations, patients, the general public, and Congress – about needs and opportunities related to the NIAMS mission. The plan is intended to guide, not prescribe, investigators in their exploration of scientific problems that bear on the health of the bones, joints, muscles, and skin. Although NIAMS will continue to commit the majority of its extramural budget to funding investigator-initiated research ideas, the Institute recognizes the need for flexibility to adapt to emerging science.

Like all NIH Institutes and Centers (ICs), in addition to managing its own budget allocation, NIAMS employs agency-wide approaches and resources, drawing from the NIH Common Fund and other resources available to all ICs to support cross-cutting research and to address infrastructure needs not unique to any IC. NIAMS also continues to partner with a variety of public and private organizations to advance the transformation of discovery to health. Through these efforts, NIAMS leverages existing resources and explores many scientific areas in ways that the Institute would not be able to do alone.

Although the NIAMS Long-Range Plan for FY 2015-2019 covers the Institute's five disease- or tissue-specific areas noted above, modern biomedical and behavioral research crosses traditional scientific boundaries, as we discover that diseases and conditions share molecular, physiological, and behavioral components. Thus, NIAMS

recognizes that trans-disciplinary and inter-disciplinary approaches are essential to unraveling disease origins, identifying and understanding co-morbidities, as well as for developing effective treatments.

The NIAMS Long-Range Plan for FY 2015-2019 also highlights needs and opportunities that are relevant to many NIAMS research communities, through four cross-cutting themes:

Health Disparities. Whether common or rare, many diseases and conditions within the NIAMS mission affect some individuals disproportionately. This Plan targets the study of biological mechanisms, health outcomes, and scientific workforce demographics as key points for potential intervention to reduce health disparities and their impacts.

Training and Career Development. Biomedical and behavioral research is a human endeavor, and NIAMS is committed to keeping the talent pipeline strong and diverse. Fostering early-stage investigators is a key NIAMS goal, as is the support of a range of research training and career development programs that address the needs of mid-career scientists.

Information Dissemination and Outreach. NIAMS-supported research is only useful if it is translated to better health in people, underscoring the vital need to embrace dissemination and outreach to diverse audiences. NIAMS will continue working closely with stakeholders to fulfill this important goal.

Collaborations. NIAMS works closely with other NIH components to advance research in areas of shared interest. Through participation in a number of trans-NIH working groups, the Institute ensures that diseases within its purview are included in trans-NIH initiatives, leverages NIAMS resources, and avoids duplication of effort with other NIH entities.

Importantly, the NIAMS Long-Range Plan for FY 2015-2019 is a map, not a destination. The Institute is committed to communicating transparently with its stakeholders to maximize the careful stewardship of federal funds and to respond appropriately to emerging needs in science and health.

INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research into causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; training of basic and clinical scientists to carry out this research; and dissemination of information on research progress in these diseases. It is critical to revisit program areas periodically because research needs, opportunities,

and challenges change. The NIAMS Long-Range Plan for FY 2015-2019 will facilitate communication between the Institute and its many constituents – scientific communities, health care providers, health advocacy organizations, the general public, and Congress – about needs and opportunities related to the NIAMS mission.

NIAMS supports a broad range of research, training, and information dissemination activities. Some conditions within the NIAMS mission are very common, while some are rare – affecting only a few thousand people worldwide. The 2010 Global Burden of Disease data[1] has yielded numerous publications regarding the extent to which many conditions within the NIAMS mission affect society. For example, the 30 leading causes of disability in the United States, as measured in years lived with disability (YLDs), include low back pain, other musculoskeletal disorders, osteoarthritis, rheumatoid arthritis, eczema, and osteoporosis/inadequate fracture repair (ranked as numbers 1, 3, 9, 23, 25, and not listed, respectively).[2] The high ranking of "other musculoskeletal disorders" casts light on the significant burden on society from diseases covered by the NIAMS mission. As noted in the Global Burden of Disease publication, "other musculoskeletal disorders" include relatively common disorders, such as ankylosing spondylitis, fibromyalgia, psoriatic arthritis, scleroderma, and systemic lupus erythematosus, as well as rare diseases, such as the autoinflammatory condition Bechet's disease, various forms of juvenile arthritis, the inflammatory muscle disease polymyositis, rare systemic connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndromes, and different types of vasculitis (e.g., polyarteritis and Wegener's granulomatosis).[3] Arthritis and musculoskeletal and skin conditions of all types affect people of all ages and of all racial and ethnic backgrounds. Combined, they afflict tens of millions of Americans, cause tremendous human suffering, and cost the U.S. economy billions of dollars in health care costs and lost productivity.

The purpose of the NIAMS Long-Range Plan for FY 2015-2019 is to continue to promote exploration of ideas and encourage new research directions as needed. Although NIAMS will continue to devote the majority of its extramural budget toward funding the best investigator-initiated research ideas, the Institute recognizes the need for flexibility in serving the scientific community in the best possible ways. The Plan brings attention to many areas that could be explored in coming years to propel research progress related to improved understanding, diagnosis, treatment – and ultimately, prevention – of diseases within the NIAMS mission.

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[1] Murray CJ, et al. Lancet. 2012. PMID: 23245608
[2] US Burden of Disease Collaborators. JAMA. 2013. PMID: 23842577
[3] Smith E, et al. Ann Rheum Dis. 2014. PMID: 24590181

The Plan is not comprehensive; it does not mention every research area or disease of interest by name. As a broad scientific outline for NIAMS, however, it informs the Institute's priority-setting process while enabling the Institute to adapt to rapidly changing biomedical and behavioral science landscapes.

Through responsible stewardship of taxpayer dollars, NIAMS promotes exploration of a broad spectrum of highly meritorious research. To facilitate this process, the Institute will continue to partner with a variety of public and private organizations to advance research within mission-relevant areas. Through these efforts, NIAMS will be able to leverage existing resources and explore many scientific areas in ways not possible on its own. By supporting research that is complementary to programs supported by other NIH Institutes and Centers (ICs), NIAMS will broaden the impact of scientific advances and continue toward the goal of improving the quality of life of all Americans affected by diseases of bones, joints, muscles, and skin.

CROSS-CUTTING TOPICS

The NIAMS Long-Range Plan for FY 2015-2019 is organized into five disease- and tissue-specific topics – Arthritis and Rheumatic Diseases, Skin Biology and Diseases, Bone Biology and Diseases, Musculoskeletal Biology and Diseases, and Muscle Biology and Diseases – each of which is divided into categories and broad areas of potential research directions, needs, and opportunities. However, NIAMS recognizes that overlapping areas exist within each topic and fully expects many advances to arise as a consequence of research performed in additional fields.

This Plan also presents three cross-cutting areas that highlight needs and opportunities relevant to many of the Institute's research communities. These areas include Health Disparities, Training and Career Development, and Information Dissemination and Outreach.

I. HEALTH DISPARITIES

Most of the diseases covered by the NIAMS mission areas are chronic, and many cause life-long pain, disability, or disfigurement. They affect millions of Americans; cause tremendous human suffering; and cost the U.S. economy billions of dollars in health care costs and lost productivity. These conditions affect people of all ages, racial and ethnic populations, and economic groups. Many affect women and minorities disproportionately – both in increased numbers and increased disease severity. For example, women with systemic lupus erythematosus (SLE) outnumber men nine to one. African American women are three times as likely to have SLE as are White women, and the disease is also more common in Hispanic, Asian, and American Indian women. SLE risk genes have been identified on the X chromosome, which provides potential evidence for this autoimmune disease's sex bias. Rheumatoid arthritis, osteoporosis, and osteoarthritis (in people over 45 years of age) are also more prevalent among women, whereas certain forms of ankylosing spondylitis (inflammation of the joints in the spine) occur more frequently in men.

Socioeconomic status, education level, cultural issues, and medical practice variation are all factors that may contribute to health disparities after disease onset, potentially affecting disease progression and treatment response. Understanding the role these issues play can help inform the development of strategies to reduce outcome disparities, and that knowledge will permit early diagnosis and disease management tailored to an individual's needs.

The NIH Revitalization Act of 1993 (Public Law 103-43) requires inclusion of women and minorities in NIH-funded clinical research, unless there is appropriate justification

for not including them. Researchers need to consider factors such as sex, race, ethnicity, and socioeconomic status in the design, data collection, and analysis of clinical research studies and clinical trials. These studies serve as resources for data that could be leveraged to answer important, fundamental questions in health disparities research, including:

- Establishing the current degree of disparities, to allow a rigorous evaluation of progress toward their reduction or elimination;
- Developing standards of clinical data features for health disparities;
- Identifying areas ready for immediate study, such as those where health disparities due to minority or socioeconomic status are well documented; and
- Using administrative databases (e.g., billing, pharmacy) as a source of data associated with population groups to examine research topics such as medical compliance (e.g., adherence to taking bisphosphonates after hip surgery).

As stated above, many diseases within the NIAMS mission areas exhibit sex disparities. Enhanced attention to sex as a critical factor in basic and pre-clinical studies will help us to better understand the biology underlying sex differences, and it will provide knowledge to improve the health of women, men, girls, and boys. NIAMS supports the NIH's efforts on Studying Sex to Strengthen Science, which calls on researchers to take sex into account as they develop their research questions, design experiments, analyze data, and report results.

The following are some of the key research needs and opportunities in health disparities:

A. Biological Mechanisms

- Investigating genetic, biological, and environmental mechanisms underlying increased susceptibility to, and severity of, disease among different racial and ethnic populations, as well as among the sexes;
- Expanding research on autoimmune diseases with female preponderance and elucidate associated pathogenic pathways;
- Exploring how sex disparities in diagnosis or treatment may be related to symptom descriptions by patients, unconscious bias of physicians, or treatment response, and how physicians and researchers could be trained to compensate for these differences; and
- Understanding how comorbid conditions associated with particular groups (e.g., diabetes, kidney disease) may contribute to disparities in disease severity.

B. Health Outcomes

- Conduct behavioral research investigating cultural issues that can influence disease management and outcomes (e.g., risk behaviors and medical compliance) and incorporate findings into patient education strategies to promote adoption of healthy behaviors.
- Investigating factors that affect outcomes for rural, underserved, and minority populations, including health insurance, reimbursement-related issues, and socioeconomic factors (Examine ways that treatment protocols could be modified to better serve these populations.);
- Expanding use of electronic medical record (EMR) data to facilitate exploration of outcomes disparities for individuals with differing socioeconomic status receiving standard care, and ascertain the contribution of factors such as access to subspecialty care, missed follow-up appointments, or caregiver availability; and
- Pursuing research on diseases with significant effects on the health and quality of life of populations affected by health disparities (e.g., vitamin D insufficiency, vitiligo, and keloids).

C. Scientific Workforce

- Developing a diverse, culturally competent workforce in biomedical research and health care, toward expanding interest and commitment to reducing health disparities and
- Encouraging development of a “critical mass” of researchers actively pursuing health disparities research, either through expansion of the scope of projects to include health disparities elements, or by engaging health disparities researchers from other disciplines to initiate projects within NIAMS mission areas.

II. TRAINING AND CAREER DEVELOPMENT

NIAMS is committed to ensuring that a diverse and highly skilled workforce is available to assume leadership roles in biomedical and behavioral research. The Institute encourages and supports research trainees at all levels through use of predoctoral and postdoctoral training programs and fellowships, mentored career-development awards, and grants for newly independent investigators. NIAMS also partners with professional societies and other organizations to ensure that a comprehensive and complementary portfolio of research training opportunities is available.

Much of the research within NIAMS mission areas will require multi-disciplinary contributions to maximize its impact, and trainees should be imbued with a thorough understanding of how to work within teams and across traditional scientific silos. NIAMS

encourages investigators to design training experiences that include team science and multi-disciplinary projects, as appropriate.

NIAMS participates in trans-NIH programs to encourage early-stage investigators to begin exploring research projects on arthritis, rheumatic diseases, musculoskeletal conditions, and skin diseases. Predoctoral fellows in Ph.D. or formal dual-degree programs (M.D./Ph.D., etc.) and postdoctoral fellows may be eligible for individual Ruth L. Kirschstein National Research Service Awards (NRSAs). Universities and other eligible organizations can apply for institutional NRSAs that provide support for both predoctoral and postdoctoral trainees.

In addition to encouraging trainees to pursue research in NIAMS mission areas, the Institute employs several mechanisms to provide clinicians with protected time for research. The NIH Mentored Clinical Scientist Research Development Award (K08) supports clinicians for an intensive experience in basic and translational research. The NIH Mentored Patient-Oriented Research Career Development Award (K23) is targeted to clinically trained professionals who intend to focus their research careers on patient-oriented research. The NIH Mid-career Investigator Award in Patient-Oriented Research (K24) provides protected time for mid-career clinicians to conduct patient-oriented research and to act as mentors for junior clinical investigators. Clinicians are also encouraged to apply to the NIH Loan Repayment Program (LRP), which helps pay for qualified student-loan debt. NIAMS will continue to use these mechanisms to help ensure a robust pipeline of clinical researchers, and the Institute remains interested in developing partnerships with research and professional societies to support early-stage and new investigators as they make critical career-stage transitions.

NIAMS also participates in programs focused on support for new and early-stage investigators, a high priority at NIH. For example, the Pathway to Independence Award (K99/R00) program is designed to facilitate a timely transition from a mentored postdoctoral research position to a stable, independent research position at an earlier stage than is currently the norm. In addition, early-stage investigators are given special consideration during review as well as during NIAMS funding decisions.

Read more information on these programs, as well as other focused on research training and career development.

Through an ongoing assessment of needs and opportunities, NIAMS has maintained a multi-dimensional approach to training and career development. The Institute's commitment to develop and nurture a healthy pipeline of biomedical researchers

focused on the diseases and disorders within NIAMS mission areas will advance science in the 21st century.

III. INFORMATION DISSEMINATION AND OUTREACH

The driving force behind NIAMS-funded research is to improve the lives of those who are affected by diseases and conditions of bones, joints, muscles, or skin. Sharing information about research progress and conducting outreach to multiple audiences continue to be essential components of the NIAMS mission. The Institute is committed to communicating research advances to all segments of the public.

A. Information Dissemination

The Institute is dedicated to working closely with grantee institutions to disseminate research findings to varied audiences via multiple venues. Key priorities include:

- Enhancing access to trustworthy and audience-appropriate health information in multiple languages and formats, with an increasing emphasis on electronic offerings (see "Information Dissemination and Outreach Resources") and
- Raising awareness of NIAMS-supported research through plain-language descriptions that are widely shared via multiple channels, including social media.

NIAMS will continue to support and operate the NIAMS Information Clearinghouse and the NIH Osteoporosis and Related Bone Diseases ~ National Resource Center. Both clearinghouses distribute health-education materials to patients, allied health professionals, researchers and scientists, voluntary and professional organizations, underserved and at-risk populations, the media, and the general public. The NIAMS Information Clearinghouse provides materials on diseases and conditions of bones, joints, muscles, and skin in a variety of formats and languages.

The National Resource Center provides an important link to resources and information on metabolic bone diseases including osteoporosis, Paget's disease of bone, and osteogenesis imperfecta. The National Resource Center is supported by NIAMS, with contributions from the National Institute on Aging, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the NIH Office of Research on Women's Health, and the HHS Office on Women's Health.

Social media has increasingly become the primary avenue through which people receive news and information, as well as a main vehicle for interacting with individuals and organizations alike. NIAMS has fully integrated social media into its information-dissemination program. The Institute posts regular updates to Twitter (@NIH_NIAMS)

and Facebook (NIH.NIAMS), featuring NIAMS health publications, news and announcements, and other informational resources. NIAMS will continue its efforts to reach even more people via social-media channels, and the Institute will explore the use of other social media tools, such as Twitter chats, to increase direct interaction with its audiences.

Information Dissemination and Outreach Resources

What sort of publications does NIAMS offer?

NIAMS develops health-information materials for patients and their families, health care providers, and the general public. NIAMS offers many of its publications in easy-to-read English formats, as well as in several other languages including Spanish, Chinese, Korean, and Vietnamese. In addition, NIAMS makes available several publications in audio formats for visually impaired individuals and/or those with limited literacy skills. A separate Spanish web portal and Asian language landing page enable users to easily access publications in different languages.

How do I order publications from NIAMS?

Please visit the NIAMS website or call 877-226-4267 (TTY 301-565-2966) (toll free call) or e-mail NIAMSinfo@mail.nih.gov. Publications are free.

How can I stay informed about NIAMS activities?

Each month, the Institute produces the NIAMS Update, an electronic digest for those interested in the latest scientific news and resources on diseases of bones, joints, muscles, and skin. Please visit the About page on the NIAMS website for more information. The Institute also disseminates the NIAMS Multicultural Outreach News, an online digest for those interested in information and resources for multicultural communities. In addition, updates can be received via Twitter and Facebook .

Looking ahead to other electronic communication efforts, NIAMS is exploring conversion of print publications to digital formats and use of electronic publications. The

Institute is also exploring a NIAMS website redesign, including enhancement of a mobile-friendly version.

B. Outreach

The Institute is dedicated to engaging the public and encouraging broad participation and input in NIAMS and NIH activities. Long-range plans in this area include:

- Increasing visibility of NIAMS as a leading resource for research-based information on diseases and conditions of bones, joints, muscles, and skin and
- Expanding understanding among scientists and students about careers and training opportunities in biomedical research fields in NIAMS mission areas, particularly in underrepresented communities.

The Institute works closely with the NIAMS Coalition to share the latest research advances and related developments, as well as to foster dialogue on future paths and directions of NIAMS-funded research. The NIAMS Coalition is an independent entity consisting of a large group of professional and voluntary organizations that work to raise awareness about research into the basic understanding, causes, incidence, treatment and prevention of diseases of bones, joints, muscles, and skin. It plays a vital role as a liaison among researchers supported by the Institute, the patients who benefit from the Institute's research investments, Congress, and the American public. The Institute will continue to engage regularly with Coalition members through teleconferences and webinars, in-person meetings, opportunities to meet with Institute leadership, and presentations at professional and voluntary meetings.

NIAMS will continue its Community Outreach Initiative, a project to ensure that research results and health information reach diverse populations. Through development and distribution of four culturally tailored health planners and other materials, people in multicultural communities nationwide receive access to health information and resources for managing conditions of bones, joints, muscles and skin. An electronic toolkit is available online to assist voluntary and professional organizations with conducting multicultural outreach. NIAMS is also implementing a Language Access Plan, as part of NIH-wide efforts to help ensure that individuals who have limited English proficiency have meaningful access to all NIAMS programs and activities.

To broaden our outreach to underrepresented groups, NIAMS has taken an active role in leading the Trans-NIH American Indian/Alaska Native (AI/AN) Health Communications and Information Work Group – a collaboration that represents 20 NIH Institutes, Centers and Offices – to coordinate NIH efforts to develop and disseminate health information targeting AI/AN communities. The Work Group has partnered with the Indian Health Service's National Community Health Representative Program on an

outreach activity to raise awareness of NIH health resources among its network of 1,600 Tribal employees who serve as lay health educators and patient liaisons in Native communities nationwide. It is pursuing a similar outreach effort with the Administration on Aging / Administration for Community Living's Title VI grantees to provide services to Native elders and caregivers.

IV. TRANS-NIH RESEARCH COLLABORATIONS

NIAMS works closely with other NIH components to advance research in areas of shared interest. Through participation in a number of trans-NIH working groups, the Institute ensures that the study of diseases within its purview are included in trans-NIH initiatives, leverages NIAMS resources, and avoids duplication of effort with other NIH entities. NIAMS chairs the Federal Working Group on Bone Diseases, a group of representatives from federal agencies concerned with bone health. NIAMS also leads the Lupus Federal Working Group, established by NIH on behalf of the HHS Secretary. NIAMS supports two of NIH's six Wellstone Muscular Dystrophy Cooperative Research Centers and shares responsibility for the Muscular Dystrophy Coordinating Committee with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Heart, Lung, and Blood Institute (NHLBI). NIAMS has played a leading role in the NIH Patient Reported Outcomes Measurement Information System (PROMIS) Initiative, a program supported by the NIH Common Fund, which is developing and disseminating tools to enhance measurement of patient-centered outcomes in clinical research, such as pain (see box, "Pain Research at the NIAMS"). In collaboration with the National Institute on Aging (NIA), NIAMS leads the Osteoarthritis Initiative, a public-private partnership between NIH and the private sector to improve diagnosis and monitoring of osteoarthritis and foster development of new treatments. In 2014, NIAMS joined with several NIH Institutes participating in the Accelerating Medicines Partnership (AMP), an initiative sponsored by NIH, biopharmaceutical companies, and several non-profit organizations to transform the current model for developing new diagnostics and treatments. AMP is conducting pilot projects in three disease areas, one of which is autoimmune disorders. Together with the National Institute for Allergy and Infectious Diseases, NIAMS is leading the AMP program in rheumatoid arthritis and lupus. NIAMS also is a member of the NIH Pain Consortium that promotes trans-NIH collaboration on pain research activities (see "Pain Research at NIAMS").

Pain Research at NIAMS: Pain is an important aspect of many diseases within the NIAMS portfolio. While there have been many developments in understanding of acute pain and how it is treated, this knowledge has not been easily translated into interventions for chronic pain, which is a serious public health problem. NIAMS funds a variety of studies related to the diagnosis and treatment of conditions that are associated with chronic pain. Although some are common – such as osteoarthritis, rheumatoid arthritis, chronic low back pain and fibromyalgia – many others, including certain pediatric autoimmune or autoinflammatory diseases, affect only a few thousand people globally. Research activities include expanding the NIH Common Fund-supported Patient Reported Outcomes Measurement Information System (PROMIS) to allow clinicians and researchers to assess pain objectively in children. Other studies are addressing the interplay between psychological and behavioral factors and patients' pain experience in the clinical care of musculoskeletal and rheumatic diseases and injuries. NIAMS also supports clinical trials and clinical-planning grants focused on the development of non-opioid-based therapies and combination therapies (e.g., cognitive behavioral therapy with drug therapy) for chronic pain. Researchers are also exploring the role of the immune and the nervous systems in chronic pain and considering ways to translate results into new therapies.

In light of the Institute's considerable investment in pain research, NIAMS coordinates its efforts with those of other ICs through participation in the trans-NIH Pain Consortium. For example, NIAMS partnered with the National Center for Complementary and Alternative Medicine (NCCAM) to coordinate a Pain Consortium Task Force to develop research standards for chronic low-back pain. The Task Force report, which was published in 2014, is available through the Pain Consortium website. NIAMS also partners with several other ICs to support the Pain Consortium's Centers of Excellence in Pain Education. These Centers act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools.

DISEASE AND TISSUE-SPECIFIC TOPICS

I. ARTHRITIS AND RHEUMATIC DISEASES

NIAMS Arthritis and Rheumatic Diseases programs address basic, translational, and clinical research in immune-mediated arthritis and autoimmune-related acute and chronic disorders. These include, but are not limited to, the adult diseases of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE, or lupus), crystalline-induced diseases (gout, calcium pyrophosphate dihydrate crystal deposition disease, hydroxyapatite crystal disease), the spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis), reactive, enteropathic and infectious arthritis, scleroderma, vasculitides (giant cell arteritis, polymyalgia rheumatica, granulomatosis with polyangiitis), and Sjögren's syndrome. Others include pediatric diseases, such as juvenile idiopathic arthritis, periodic fever syndromes, and juvenile lupus, which generally have a more severe onset and disease course than does the adult form of lupus. In particular, these programs support studies focused on the basic biology of autoimmunity and inflammation, to better understand molecular mechanisms underlying these processes and with the goal of finding ways to improve patient-centered outcomes. NIAMS is pursuing research opportunities that employ genetic and genomic research, clinical trial design and conduct, chronic pain, and biopsychosocial aspects of diseases within this portfolio, as well as identification of risk factors for these disorders. [Note: Osteoarthritis is covered in Bone Biology and Diseases and Musculoskeletal Biology and Diseases.]

A. Arthritis and Rheumatic Diseases: Genetics and Genomics

Rheumatologists have long recognized the incidence of many rheumatic diseases within families and certain ethnic populations, pointing to some role of genetic risk. Scientists' perseverance in gathering biospecimens and clinical histories from patients and their relatives – along with the explosion of knowledge and techniques in genetics and genomics – have opened new research avenues. Emerging opportunities to study genes and pathways, epigenetics, and gene-environment interactions are expected to provide novel insights into disease mechanisms, and ultimately lead to development of better tools for diagnosis, prognosis, prevention, and treatment.

1. Genes and pathways, epigenetics, and gene-environment interactions

Genome-wide association studies (GWAS) have led to significant advances in understanding complex rheumatic disorders by facilitating identification of common genetic variants of modest effect that influence disease risk. Despite promising results, the functions of identified variants remain largely unknown, and follow-up studies are needed to understand the mechanisms by which they may contribute to biology and

disease. A growing body of data generated through efforts such as the Encyclopedia of DNA Elements (ENCODE) Project and the NIH Epigenomics Program has enabled researchers to extend results of GWAS studies through genome-wide analysis of transcription, chromatin organization, and epigenetic marks. Findings indicate that the majority of variants identified by GWAS fall within the non-protein-coding regions of the genome.

Recent data suggest that environmental factors may directly influence disease risk by interacting with the genome to alter gene expression. Analyses of gene-environment interactions are expected to provide information about the relationships between rheumatic diseases and alterations in DNA methylation and chromatin remodeling, RNA transcripts and their encoded proteins, and microRNAs. Research on genes or variants that interact with environmental factors (e.g., gut microbes, dietary components, infectious agents) to trigger disease may provide important insights into the development, progression, and severity of rheumatic diseases.

Broad areas of potential research directions include:

- Understanding the biology of genetic variants identified through GWAS, including the role of gene regulation, non-coding RNA [e.g., microRNA and long non-coding RNAs (lncRNAs)], and epigenetic regulation, in relevant cell types;
- Leveraging publically available data resources such as the ENCODE Project and NIH Epigenomics Program, as well as novel computational and bioinformatics tools, to guide or prioritize functional analyses of causal variants;
- Expanding on next-generation sequencing (e.g., through whole-genome sequencing) and other novel technologies to identify a full spectrum of variants associated with disease susceptibility;
- Applying novel strategies to dissect the major histocompatibility complex (MHC) loci associated with rheumatic diseases;
- Applying novel gene-editing techniques, such as CRISPR/Cas or TALENs, to assess the function of candidate variants in relevant model systems (e.g., induced pluripotent stem cells), and knock-in or knockout (e.g., RNAi) in vitro and in vivo models;
- Studying gene-gene, gene-protein, and gene-environment interactions and exploring single-cell genomics such as RNA-sequencing in relevant tissues and cell types; and
- Exploring crowdsourcing or other novel approaches to expand patient sample sizes and acquisition of longitudinal data, and to enhance broad sharing of data to facilitate genetic and genomic studies.

2. Translation of genetic and genomic research from bench to bedside

The rapidly progressing fields of genetics and genomics offer powerful tools for drug discovery and for studies of the influence of genomic variations on drug response by correlating gene expression or SNPs with drug efficacy or toxicity. The application of genomic approaches to therapies used in arthritis and rheumatic diseases holds great promise for personalized medicine, in which genetic information can facilitate diagnoses, and treatment can be guided by an individual's unique genetic makeup (see "Using Genetic Analysis for Drug Discovery in Rheumatoid Arthritis").

Using Genetic Analysis for Drug Discovery in Rheumatoid Arthritis: Many biological pathways, including those of the immune system, are perturbed in people with rheumatoid arthritis (RA). Determining which of these pathways should be the focus of drug development efforts is an enormous challenge, because only some of them cause disease. Using a systematic strategy that integrates genetic findings with diverse genomic and biologic data, an international team of researchers has shown that a number of molecular targets of known drugs are RA disease genes revealed by comprehensive genetic analyses, suggesting that some of these drugs might be re-purposed for RA treatment. Researchers have also uncovered several new candidate drug targets based on genetic and genomic information. This research highlights the potential of human genetic approaches to shed light on genes and pathways that contribute to the onset of disease, and points to the application of genetics as a valuable tool to prioritize molecular targets for novel therapeutic testing in RA and other related complex diseases.

For further information see Arthritis Genetics Analysis Aids Drug Discovery.

Broad areas of potential research directions include:

- Applying novel, robust genetic and genomic approaches to understand disease mechanisms and differences in treatment responses and drug toxicities;
- Elucidating the role of epigenetic mechanisms in the onset and progression of rheumatic diseases;
- Linking developments in genetics, genomics, proteomics, bioinformatics, and systems biology to clinically relevant issues, particularly prediction, prevention, and monitoring of rheumatic diseases;
- Using genetic and genomic findings to inform drug discovery and clinical diagnostics;
- Defining disease heterogeneity at the molecular level by applying functional genetic and genomic information, as well as other relevant factors, to refinement of phenotypes and subcategories of complex diseases;

- Developing and validating clinically useful models for predicting disease risk, progress, and prognosis; and
- Exploring the potential of gene-based therapies including gene-silencing (e.g., small interfering RNAs with conjugates) and overexpression approaches to treat or prevent disease.

B. Arthritis and Rheumatic Diseases: Mechanisms of Disease

1. Immune and inflammatory mechanisms

Increased knowledge of basic functioning of the immune system, and in particular, the fundamental biology of autoimmunity, has advanced our understanding of arthritis and other rheumatic diseases. Two arms of the immune system – the innate and adaptive immune systems – coexist as protective and as potentially injurious forces. These two systems have evolved to protect humans from environmental insults and to detect early damage to cells. Improved understanding of the immune system, the complex interplay between innate and adaptive immunity, as well as interactions between the immune system and various tissues in normal and pathological conditions will lay the groundwork for future therapies for autoimmune diseases.

a. Innate immunity

The innate immune system is the body's first line of defense and reacts quickly and broadly to danger by identifying damaged cells and invading pathogens such as bacteria and viruses. It consists of anatomical barriers, networks of soluble mediators, and effector cells.

The innate immune system uses a limited number of receptors, called pattern recognition receptors (PRRs), to recognize microbial products called pathogen-associated molecular patterns, or PAMPs, as well as mislocalized or damaged molecules from the body called damage-associated molecular patterns, or DAMPs, that arise during cell stress.

The first identified, and best characterized, PRRs are toll-like receptors (TLRs), which are membrane-bound proteins expressed on the cell surface and in endosomal compartments. Other types of PRRs include C-type lectin receptors (CLRs), found in both membrane-bound and secreted forms and a more recently discovered class of PRRs that detects microbial and danger signals inside of cells. The latter includes NOD-like receptors (NLRs), retinoic acid-inducible gene I-like receptors (RLRs), and cytosolic DNA sensors such as members of the AIM2 family. After PRR activation, various signaling cascades initiate or shape an inflammatory response. For example, after recognizing a PAMP or DAMP, a number of NLRs are known to form the framework for

multi-protein cytosolic platforms called inflammasomes, which orchestrate early inflammatory processes. The resulting inflammatory cascade recruits immune cells to sites of infection or damage, triggering expression of molecules needed for the transition to adaptive immunity.

An example of how the innate immune system may contribute to disease is described in "Novel Mechanism for the Development of Inflammation and Tissue Damage in Lupus."

Broad areas of potential research directions include:

- Elucidating the role of the human mucosal and skin microbiome in the etiology of rheumatic diseases;
- Studying the role of innate immune system components – DAMPs, PAMPs, PRRs, inflammasomes, and associated signaling pathways – on the initiation and propagation of autoimmune and autoinflammatory diseases;
- Expanding understanding of cross-regulation between components of the innate and adaptive immune systems in inflammation and rheumatic diseases (e.g., TLR-induced maturation and activation of plasmacytoid dendritic cells to produce type I interferon; direct regulation and activation of TLR-expressing T and B cells in response to TLR ligands);
- Studying involvement of a wide range of hematopoietic and other cell types in rheumatic diseases. Examples include – but are not limited to – macrophages, monocytes, neutrophils, platelets, dendritic cells, innate lymphoid cells, mast cells, basophils, eosinophils, fibroblasts, and synoviocytes;
- Understanding the contribution of dysregulated cellular processes (e.g., citrullination, cell death, autophagy, unfolded protein response) in development and progression of autoimmune disorders; and
- Improving understanding of differences within the molecular and cellular components that mediate specific systemic autoimmune diseases.

Novel Mechanism for the Development of Inflammation and Tissue Damage in Lupus: Research suggests that abnormalities or dysregulation of basic cellular functions and interactions of a variety of immune cell types may be centrally involved in lupus. Neutrophils, abundant, yet short-lived white blood cells involved in the innate immune response, are thought to contribute to damage observed in lupus. Recent studies have indicated that neutrophil death by a mechanism called NETosis was the likely source of material that elicited an autoimmune response. NETosis occurs when dying neutrophils release a web of DNA coated with anti-microbial proteins, forming a structure called a neutrophil extracellular trap (NET). Researchers suspect that lupus is characterized by an imbalance between NET formation and NET clearance, leading to creation of stable immunogenic material that can activate other immune cells and, ultimately, cause tissue damage. A recent study, using a combination of both human and animal research, described a novel mechanism, enhanced in people with lupus, through which NETs activate inflammation in tissues, thus describing a link between NETs and tissue damage in humans. Although molecular mechanisms through which NETs may be promoting inflammation and tissue damage in lupus are just beginning to be identified, such findings may eventually provide novel targets for treatment development leading to improved patient care and outcomes.

Reference:
Kahlenberg JM, et al., J Immunol. 2013. PMID: 23267025

b. Adaptive immunity

In contrast to the innate immune system, the adaptive immune system provides more specific, targeted, and sustained responses. Successful adaptive immunity against a broad range of pathogens depends on the body's ability to produce randomly generated, diverse receptors on the surface of lymphocytes. Because of the enormous number of antigens that the body routinely encounters, and their potential similarity to "self" components, the adaptive immune system is at risk of producing self-reactive (autoreactive) cells that can trigger autoimmunity. The process of immune tolerance addresses this problem by either removing autoreactive cells from the system or by diminishing their reactivity enough to prevent disease. When there is a breach or dysregulation in immune tolerance, autoimmune disease can occur. Thus, a better understanding of the mechanisms of adaptive immunity and autoimmune diseases may enhance development of antigen-specific and/or autoreactive cell-specific therapies that leave protective, global immune function intact.

Broad areas of potential research directions include:

- Clarifying the role of the major histocompatibility complex and antigen-presenting cells in autoimmunity;
- Further defining the role of T cell and B cell subsets and functional plasticity in immune responses and autoimmune rheumatic diseases;
- Expanding understanding of autoantigen expression in rheumatic diseases, including the role of metabolic and other changes (e.g., citrullination) in tissue or organ environments that lead to autoantigen production;
- Developing novel techniques to identify autoantigens involved in rheumatic diseases;
- Defining and characterizing mechanisms that control tolerance to self and autoantibody production;
- Exploring mechanisms of remission and exacerbation of autoimmune diseases;
- Investigating the established roles of B cells in autoimmune diseases (autoantibody production), as well as their more newly elaborated functions (antigen presentation and co-stimulation during initiation of immune responses, and the release of inflammatory and immunomodulatory cytokines); and
- Elucidating mechanisms by which sex hormones, sex-specific gene products (e.g., X and Y chromosome products), and other sex-specific factors (e.g., pregnancy) influence immune functions, in an effort to understand why autoimmunity is so much more common in women.

c. Inflammation and inflammatory mediators

Chronic inflammation is a characteristic of many autoimmune diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory myopathies, and lupus. Inflammation causes swelling, pain, and organ damage. Research advances detailing molecular and cellular contributors to this condition have provided critical insights into the potential causes of inflammation. Understanding both triggers and amplifiers of inflammation will help researchers design targeted therapies.

Broad areas of potential research directions include:

- Exploring the role of specific cytokines, chemokines, eicosanoids and other lipid-based signaling molecules, proteases (including neutral proteases from mast cells), inhibitors of proteases, as well as receptors for these molecules in autoimmune and inflammatory components of rheumatic diseases;
- Conducting further research on the development and biological functions of T cell subsets, as related to the inflammatory process in rheumatic diseases (e.g., the role of regulatory T cells in ameliorating inflammation);

- Identifying and characterizing molecular mechanisms that either resolve or dampen inflammation (e.g., anti-inflammatory cytokines, chemokine/chemokine receptors and "decoys," lipid-derived mediators, leukocyte apoptosis);
- Investigating the influence of immune-cell trafficking on disease mechanisms, including the identification of key components of leukocyte migration from the vasculature to surrounding tissues (extravasation), and examination of the roles of the adhesion molecules and chemoattractants that mediate cell trafficking;
- Studying potential environmental triggers of pathogenic pathways and inflammation, such as infection (as in Lyme disease), occupational exposures, smoking, diet, and inflammation-associated factors; and
- Enhancing understanding of the genetics and mechanisms of autoinflammatory disorders (e.g., role of cytokines such as IL-1 and TNF-alpha) to improve diagnosis and treatment of these diseases.

d. Pain

Pain is one of the most important issues affecting quality of life for patients with rheumatic diseases. Research on the biological mechanisms of pain in rheumatic diseases may lead to new approaches for pain management.

Broad areas of potential research directions include:

- Investigating interactions involving the plasticity of the peripheral and central nervous system – and the plasticity of the inflammatory system – which may contribute collectively to the development and perpetuation of chronic pain;
- Characterizing reversible and permanent biochemical, inflammatory, autoimmune and anatomic changes that cause, or are caused by, chronic pain;
- Identifying a set of biological, behavioral, genetic, epigenetic, cognitive, psychological, and social factors (the “exposome”) that makes an individual susceptible to chronic pain, the transition from acute to chronic pain, or the transition from pediatric to adult pain;
- Studying the heterogeneity and epidemiology of pain syndromes to understand their genetic, epigenetic, environmental and social risk factors, the mechanisms by which they develop, and variations in phenotype;
- Exploring and validating both existing and new tools that will allow for accurate diagnosis and optimized, personalized treatment of chronic pain conditions;
- Exploring the use of appropriate animal models of chronic pain to better understand its pathophysiology and etiology and to develop behavioral measures;

- Developing and validating tools to identify individuals at risk for chronic pain and facilitate early identification of pain to enable early intervention and prevent transition to a chronic state; and
- Developing novel therapeutic approaches to treat chronic pain conditions that encourage the development of analgesic drugs, including non-opioid-based drugs, personalized therapeutics, and behavioral interventions.

2. Target organ damage

Manifestations of rheumatic diseases can be diverse and may affect many organs and organ systems, including skin, joints, and other internal organs such as the kidneys, heart, lungs, blood vessels, and brain. Although immune dysregulation plays a major role in these diseases, structure and function of target organs such as the vasculature may also contribute significantly to the development of tissue damage and clinical disease. A better understanding of mechanisms of tissue damage may suggest how to modify contributing factors and lead to approaches to minimize or prevent some of the most serious complications of autoimmune disease.

Broad areas of potential research directions include:

- Exploring interrelationships between immune response components (both innate and adaptive) and target tissues or organs (e.g., synovium in rheumatoid arthritis, kidney in lupus) in normal and pathological conditions;
- Investigating the role of non-immune mechanisms (e.g., hypoxia, fibrosis, and metabolic changes) in tissue injury;
- Characterizing and understanding how autoantibodies cause disease;
- Elucidating the effector mechanisms of tissue damage (e.g., complement, cytokines, and immune complexes);
- Investigating how organ responses may sustain inflammatory disease;
- Identifying associations between chronic inflammation and the initiation and progression of cardiovascular disease in arthritic and rheumatic diseases;
- Understanding the roles of blood vessels and vascular endothelium in the pathogenesis of inflammatory rheumatic diseases; and
- Investigating the function of neurons that innervate lymphoid tissues and characterizing links between immune dysfunction and nervous system involvement in rheumatoid arthritis, lupus, scleroderma, and other rheumatic diseases.

C. Arthritis and Rheumatic Diseases: Preclinical and Translational Research

Unraveling the complexity of rheumatic diseases requires an understanding of how disease initiation and progression are integrated, toward development of effective and targeted interventions. Much of this research is conducted in model systems (see below) which leads to further refinement of therapeutic approaches and design before human testing.

Recent progress in developing molecular and genetic tools (e.g., single-cell analysis, 'omics technologies, genome editing, and sequencing techniques for identifying bacterial isolates) for basic research has facilitated disease-specific investigations (see "Role of the Microbiome in Health and Disease"). Preclinical and translational studies are expected to advance knowledge of underlying mechanisms and facilitate development of therapies for application in clinical practice.

Role of the Microbiome in Health and Disease: Researchers are investigating the potential connection between health, disease, and the human microbiome – the entire population of microorganisms that inhabit the human body. Studies suggest that the microbiome plays an important role in maintaining good health, most likely by keeping populations of pathogenic organisms at appropriate levels. In addition, changes in the composition of the microbiome have been associated with a number of diseases. In a recent translational research study, scientists compared gut microbes of people with new-onset, untreated rheumatoid arthritis to gut microbes present in healthy controls, people with rheumatoid arthritis who were receiving treatment, and people with psoriatic arthritis. The researchers found that the bacterium Prevotella copri was more abundant in patients with new-onset, untreated rheumatoid arthritis than in the other groups, suggesting that the bacterium contributes to development of the disease. The discovery establishes a link between a specific type of gut bacteria and the onset of rheumatoid arthritis, provides a basis for further investigations of the role of the microbiome in rheumatoid arthritis, and holds promise for advancing diagnosis, treatment, and prevention.

For further information, see Gut Microbes Linked to Rheumatoid Arthritis.

1. Model systems

Model systems aim to define disease mechanisms, as well as to design and test approaches to prevent disease onset and progression. Animal models offer some of the best systems for detailed phenotyping of various diseases and conditions, enabling scientists to identify human disease-related genes and gain a better understanding of how these disease genes function. Current mouse models focus on immune-cell function and can recapitulate many aspects of human diseases (e.g., rheumatoid

arthritis and lupus), which provides important information about pathogenic and therapeutic pathways and their interactions. Ex vivo or in vitro cell-based systems may also serve as important experimental models for studying arthritis and rheumatic diseases.

Given the complexity of immune responses, etiologic and mechanistic questions about disease are difficult to answer. By integrating large amounts of research data into dynamic computer-based models, systems biology approaches can be used to better understand, over time, interrelationships and regulation of various immune system components.

New Model for Scleroderma Research: Efforts to improve understanding of the etiology of scleroderma and to devise therapies to treat it have been hampered by a lack of proper experimental animal models that mimic this disease. In a recent advance, investigators created a mouse model for an inherited form of scleroderma, stiff-skin-syndrome (SSS). The team had already mapped the SSS genetic mutation in humans, linking it to the gene that encodes extracellular matrix protein fibrillin-1. To make an animal model, they created transgenic mice with that same mutation and showed that the mutation causes symptoms very similar to those seen in humans with SSS. The researchers presumed that the mutation perturbs the interaction of fibrillin-1 with cell surface proteins called integrins, which act as sensors of cells' external environment. The team then tested whether drugs that mimic the interaction between fibrillin-1 and integrins would reverse manifestations of disease, and found that several such agents halted disease progression in the transgenic mice. The new model will enable further therapeutic studies to advance scleroderma understanding and treatment. In addition, it provides a powerful example of how a carefully designed animal model can advance understanding of a complex disease in humans.

For further information see Novel Insights Into Causes of Scleroderma Offer Potential New Treatment Strategies.

Broad areas of potential research directions include:

- Developing clinically-relevant animal models for functional and mechanistic studies of pathogenic pathways identified by GWAS and other human genetic research;
- Developing animal models that recapitulate molecular abnormalities identified in people with autoimmune diseases to improve understanding of disease mechanisms;
- Using gene-modulation techniques (e.g., CRISPR/Cas or TALENs for genome editing) to conduct large screens for phenotypes relevant to arthritis and

rheumatic diseases (see also Genetics and Genomics section for more information);
- Creating new animal models and using existing transgenic animals/other genetically modified animal models, to study immune, inflammatory, and non-immunologic mechanisms of arthritis and rheumatic diseases;
- Combining animal models of human rheumatic diseases with systems biology approaches, to identify critical cellular and molecular pathways involved in disease causation, and to facilitate the identification of therapeutic targets (Possible areas include central nervous system-endocrine-immune interactions that contribute to disease mechanisms and clinical symptoms.);
- Developing models for chronic manifestations of disease (e.g., models to investigate the role of mast cells in chronically inflamed tissues); and
- Developing new and improve existing ex vivo tissue and organ models for studying arthritis and rheumatic diseases.

2. Therapy development

Advances in immunology, molecular biology, and genetics are yielding an emerging set of therapies for arthritis and rheumatic diseases. The goal of NIAMS-supported research is multifold: to ensure a continuous supply of new targets for intervention, to understand mechanisms of action of new and existing drugs, and to develop adequate clinical trial methodologies to test these mechanisms. The Accelerating Medicines Partnership, described in the box "Accelerating Drug Development," is an example of how NIAMS aims to ascertain and define shared and disease-specific biological pathways that researchers can study to identify relevant drug targets for treating autoimmune diseases.

Broad areas of potential research directions include:

- Building on the successful treatment of rheumatoid arthritis with disease-modifying anti-rheumatic drugs, particularly early interventions to prevent progression to severe disease and tissue damage, toward the development of therapies for other arthritic and rheumatic diseases (e.g., lupus, scleroderma, ankylosing spondylitis, and other spondyloarthropathies);
- Creating therapeutic strategies to target immune dysregulation in arthritis and rheumatic diseases;
- Developing approaches to prevent autoimmune diseases and promote immune tolerance (e.g., by screening for factors that promote desired immunological outcomes in B cells);

- Exploring tissue-remodeling pathways involved in end organ damage to better understand pathophysiology and etiology of rheumatic diseases, and to identify new therapeutic approaches;
- Fostering pharmacogenetic and pharmacogenomics research to investigate the molecular basis of individual therapeutic response using robust genetic and genomic approaches;
- Exploring integration of genetic and genomic analyses with molecular and clinical diagnosis of disease in clinical care;
- Improving patient stratification to enhance translational research studies including studies of remission, disease prevention and progression, and treatment response;
- Exploring gene-based therapies including gene silencing (e.g., microRNAs, siRNA-conjugates, etc.) and overexpression approaches to treat or prevent disease; and
- Developing small-molecule drugs that target novel or known pathways.

Accelerating Drug Development: To increase the number of new diagnostics and therapies for people, and to reduce the time and cost of developing them, NIAMS is participating in the Accelerating Medicines Partnership (AMP), a collaboration between NIH, the Foundation for the NIH (FNIH), the FDA, biopharmaceutical companies, and non-profit organizations. NIAMS is contributing to the AMP program in two disease areas: rheumatoid arthritis and lupus. The program uses emerging technologies to gain an enhanced systems-level understanding of gene expression and signaling in target tissues and cells from affected end organs (synovium for rheumatoid arthritis; kidney or other tissues such as skin for lupus) and peripheral blood. Results are expected to define shared and disease-specific biological pathways, which may lead to the identification of relevant drug targets for treating rheumatoid arthritis, lupus, and related autoimmune diseases. AMP participants will make data and analyses publicly accessible to the broad biomedical community.

For further information, see:

- The Accelerating Medicines Partnership website.
- The NIAMS website for the AMP Rheumatoid Arthritis/ Systemic Lupus Erythematosus Program.

3. Biomarkers

The goal of biomarker research is to use modern approaches to discover and qualify biomarkers for the diagnosis, prognosis, and evaluation of therapies. In general, biomarkers are measured by changes in biochemical factors or genetic markers in

blood, body fluids, or tissues. For many disorders, a panel of biomarkers rather than a single biomarker may provide the most clinically useful information.

Broad areas of potential research directions include:

- Identifying changes in peripheral blood cells that correlate with activation of specific pathways in tissues during the course of arthritis and rheumatic diseases;
- Developing organ-specific biomarkers to predict disease risk preclinically and/or to monitor onset and disease progression;
- Obtaining an integrated dataset of changes at the molecular level obtained by extensive profiling of gene expression and signaling in immune and tissue-resident cells;
- Defining and testing algorithms that integrate different sets of biomarker data within an appropriate population (e.g., genetic, imaging, serologic, patient-reported) with sufficient power to facilitate personalized clinical decision-making regarding diagnostic tests, treatments, and prevention strategies;
- Expanding use of autoantibodies as models for biomarker development to identify disease subtypes, and to track disease progression and therapeutic response;
- Generating sensitive and reliable analytical methods coupled with assays that can detect multiple biomarkers in patient and control samples, toward evaluating complex systemic changes that occur in rheumatic diseases;
- Creating resources needed to transition promising biomarkers from bench to clinic using state-of-the-art statistical, analytical, and computational methods; and
- Developing validated and standardized outcome measures to enable better assessment of biomarkers and success of interventions.

4. Imaging

Imaging early or late changes of disease in target organs is increasingly important for characterizing disease status and determining responses to therapies. Advanced imaging technologies are providing insights into anatomic changes in disease states. For example, magnetic resonance imaging (MRI) has detected structural pathology in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Broad areas of potential research directions include:

- Using and enhancing intravital microscopy and improved fluorophores to gain new insights into cellular interactions and potential mechanisms of disease;

- Enhancing detection and quantitative measurements of structural pathology and inflammatory activity with MRI, ultrasound, optical or positron emission tomography (PET), for assessing arthritis and rheumatic diseases;
- Applying modern high-sensitivity and high-resolution imaging techniques to the diagnosis of arthritis and rheumatic diseases;
- Investigating the use of non-invasive imaging technologies in functional studies of disease prognosis and progression, potentially in association with biomarker qualification;
- Developing novel imaging technologies to enable analysis of soft tissues, including heart, blood vessels, kidney and brain, to assess end-organ damage in rheumatic diseases;
- Improving safety of imaging approaches used in clinical practice; and
- Developing ultrasound techniques (including 3D) to guide treatment decisions about inflammatory joint conditions.

D. Arthritis and Rheumatic Diseases: Clinical Research

The complexity of rheumatic diseases, the diverse presentation and progression of many of these illnesses across patient populations, and the occurrence of multiple rheumatic diseases in the same person, creates significant challenges in the diagnosis and management of these conditions. Thus, clinical characterization of disease subtypes is critical to assessment of epidemiological data and efficient design of clinical trials in these disease areas. NIAMS supports clinical research ranging from epidemiological studies to observational studies to clinical trials designed to further understanding of these diseases and to develop effective therapies to prevent or treat arthritis and rheumatic diseases.

1. Epidemiology and health services research

The incidence, morbidity, and mortality of rheumatic diseases are important foci for epidemiological research, particularly for studying complex, systemic autoimmune diseases and co-morbidities. Health-services delivery for people with rheumatic diseases is an important example of how illnesses with low mortality can still exert significant physical and quality-of-life effects.

Research needs and opportunities related to identifying mechanisms that would enable early detection and sub-phenotyping of autoimmune diseases were discussed in greater detail at a 2010 NIAMS roundtable discussion.

Broad areas of potential research directions include:

- Defining and testing preclinical strategies to understand disease pathways in humans to facilitate individualized screening and risk detection to prevent or treat early disease;
- Combining analysis of the natural history of disease with population-based epidemiological studies to determine the prevalence of diseases and associated co-morbidities (e.g., cardiovascular disease);
- Conducting research on ways to improve access to specialized care (especially for historically disadvantaged populations) and to facilitate patient-health care system interactions for improved disease outcomes;
- Researching the effects of patient-health care system interactions in disease outcomes;
- Supporting efforts to leverage international partnerships and opportunities (e.g., cohort studies and registries) to improve diagnosis and treatment of rheumatic diseases;
- Conducting research on environmental exposures that may contribute to rheumatic diseases, including systems epidemiology research to investigate the exposome and integrate it with genomic, proteomic, and other “omics” datasets;
- Conducting research to accurately identify individuals at high risk for autoimmune disease or those with very early-stage disease to facilitate clinical studies and trials to prevent or preempt development of autoimmune disease;
- Elucidating the role of the microbiome on risk, pathology, and treatment of rheumatic autoimmune diseases;
- Conducting research to understand the role of accelerated aging/immunosenescence on the pre-disposition, expression, and co-morbidities of rheumatic autoimmune diseases;
- Focusing prevention studies on risk-factor identification and reduction strategies, and conducting early-intervention trials to prevent onset or progression of disease or tissue injury;
- Exploring interactions between rheumatic diseases and common co-morbid conditions, such as atherosclerosis, obesity, and metabolic syndrome, to design effective risk management strategies, appropriate monitoring, and evidence-based early interventions;
- Investigating the safe use of therapies, especially biologics, in pregnant women and their infants;
- Developing computer models to assess the influence of prevention and treatment strategies on outcomes and cost-effectiveness in common chronic diseases (e.g., rheumatoid arthritis); and
- Applying computational tools and mobile-health technologies to epidemiological studies of autoimmune diseases.

2. Clinical trials

Many rheumatic diseases do not respond adequately to treatment, particularly due to the diverse presentation and progression of these illnesses within a patient population, along with complex interactions of disease-relevant biological pathways. Therapies that appear to be promising through preclinical modeling and testing require clinical testing in defined patient populations, or cohorts, as well as creative approaches to design assessment of health outcomes. Recent advances in imaging technologies such as ultrasound, optical and MRI (including 3D) approaches also require testing in clinical trials to evaluate their use in diagnosis and patient care.

Broad areas of potential research directions include:

- Establishing the role (qualification) of biomarkers and surrogates to diagnose, predict, or monitor disease progression and therapeutic response (efficacy and safety);
- Employing large, systems approaches of disease modeling populated by well-defined phenotypes and qualified biomarkers, toward development of more efficient clinical trial designs (by predicting cohort size) and more informed clinical decision-making (cost-effectiveness, potential toxicity vs. prevention, quality-of-life impact over time);
- Determining whether drugs approved for rheumatic conditions can be repurposed to treat other rheumatic conditions with similar pathogenic pathways (e.g., drugs approved for rheumatoid arthritis in lupus, ankylosing spondylitis, or psoriatic arthritis);
- Conducting proof-of-concept and bridging studies of approved and available therapeutics, to address clinically important questions in rheumatic diseases;
- Investigating specific treatments and imaging approaches (including 3D), for adult and pediatric rheumatic diseases;
- Conducting research to improve outcomes for common disorders, such as gout, that are expected to worsen due to a number of factors affecting the U.S./global population (e.g., aging, obesity),
- Studying the pharmacogenomics of responders and non-responders to pharmacologic and biological interventions in rheumatic diseases, to direct therapies to appropriate subsets of patients;
- Developing and testing mechanism-based treatments (individual or combinations of drugs and biologics), strategies and/or models of rheumatic diseases that seek to prevent onset, induce remission (on or off medication), predict and address disease flare, and inform ongoing personalized treatments;
- Developing, validating, and disseminating clinical outcome measures;

- Conducting clinical studies to determine benefits of treat-to-target-trials as compared to current strategies that focus on the level of disease activity;
- Conducting studies to determine the optimal duration and intensity of treatment with FDA-approved drugs (e.g., disease-modifying anti-rheumatic drugs) or with novel therapies in development and explore the value of drug holidays and/or withdrawal of therapies;
- Designing clinical studies intended to better understand onset, initiation, progression, improvement, remission, and/or flaring of arthritic and rheumatic diseases in adults and children;
- Conducting clinical trials related to cause, prevention (e.g., vaccination to prevent herpes zoster), and treatment of system-specific pain;
- Examining the effects of adding adjunctive treatments for co-morbidities (e.g., pain, fatigue, depression) to standard therapy for rheumatic diseases in individuals with co-morbidities;
- Developing functional outcome measures for chronic pain to assess effects of treatments to alleviate pain on short- and long-term functional status;
- Using comparative effectiveness approaches to evaluate the effectiveness and safety of therapies and using combination-therapy approaches for treating rheumatic disease (e.g., compare the effectiveness of traditional therapies to biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis);
- Exploring alternative clinical-trial designs for rare rheumatic diseases (Examples include active comparators rather than placebo controls, examples from cancer trials that have small cohorts, reassessed clinical research endpoints, and long-term clinical response); and
- Expanding the involvement of clinical practice physicians in community settings in large-scale trials.

E. Arthritis and Rheumatic Diseases: Behavioral and Biopsychosocial Research

Understanding the etiology, pathogenesis, and outcomes of rheumatic diseases, as well as developing effective strategies for their prevention and treatment, requires a multifaceted approach. These endeavors necessitate collaborative research efforts that integrate approaches and perspectives from multiple disciplines.

Biomedical research on rheumatic diseases continues to yield important discoveries regarding genetic, immunologic, and other biological factors that affect these conditions. Behavioral and social science research is contributing important epidemiologic information and approaches to managing distressing symptoms of these disorders (see "Patient-centered Outcomes"). However, to date, the numbers of studies integrating behavioral, basic biomedical, and clinical rheumatology perspectives have been extremely low, limiting the potential of a biopsychosocial approach to advance research

in these diseases. Recognizing the need for collaborations to advance behavioral and biopsychosocial research, NIAMS participates in several relevant trans-NIH efforts (e.g., the NIH Pain Consortium and the National Center on Sleep Disorders Research) that allow the Institute to share information about NIAMS-funded research efforts and advances and to partner with other NIH components in areas of interest. Interdisciplinary investigations that integrate behavioral and biomedical sciences will likely enhance treatment of rheumatic diseases, reduce disability, and may shed light on complex mechanisms involved in disease processes.

Research needs and opportunities were discussed in 2010 at a roundtable on Psychosocial and Behavioral Therapies for Musculoskeletal and Rheumatic Disease Outcomes.

1. Behavioral

Broad areas of potential research directions include:

- Defining genetic and environmental influences on behaviors relevant to health and disease;
- Exploring cognition and cognitive dysfunction in rheumatic diseases, including use of brain imaging and assessment of relationships between cognition, mood disturbance, and disease activity;
- Generating theoretical models for the potential influence of stress on disease course and presentation (e.g., symptom flares) (Study the influence of stress-management techniques and interventions on illness, and study potential mechanisms of stress-illness effects);
- Studying fatigue in rheumatic diseases, focusing on epidemiological issues, potential mechanisms, prevention, and treatment;
- Investigating sleep disturbances and their relationship to disease processes, symptoms, and disability in rheumatic diseases;
- Developing animal models to elucidate behavioral mechanisms in rheumatic diseases; and
- Using mobile-health technologies (e.g., smart phones) to facilitate research on the role of behavioral factors in rheumatic diseases.

2. Psychosocial

Broad areas of potential research directions include:

- Studying biological, social, and behavioral interactions as they relate to disease onset, progression, and outcomes of rheumatic diseases;

- Defining effects of systemic and societal influences on disease progression, treatment response, quality of life, and other patient-reported outcomes in rheumatic diseases;
- Studying variability in patient outcomes, symptom perception and management, and interactions with health-care systems – related to differences in behavior, gender, ethnicity, family environment, prior trauma, education, physiology, or a combination of factors;
- Exploring behavioral factors that influence patient interactions with providers and how this experience affects treatment response and long-term outcomes;
- Examining psychosocial prevention and intervention models from other disorders (e.g., diabetes, AIDS), toward promotion of healthy behaviors and management strategies for people/patients with rheumatic diseases; and
- Addressing issues in pediatric rheumatology – including pain, psychosocial adjustment, physical functioning, and intervention.

Patient-centered Outcomes: Patient-centered outcomes (PCO) such as patient-reported outcomes (PRO) are keys to better treatment and understanding of rheumatic diseases and their impact on patients' symptoms, functioning and quality of life. Most PCO instruments have traditionally been used for disease-specific assessments, rather than to facilitate advances within or across disease comparisons. Although PROs are very popular among patients, often patient concerns and their rankings of what matters most may be very different from outcomes that physicians seek. The NIH Common Fund's Patient Reported Outcomes Measurement Information System (PROMIS) initiative was created to address these gaps by the development and validation of a psychometrically-robust PRO instrument to gather information on many health-related concerns, such as pain, fatigue, and physical functioning, across a wide range of disorders. This information will be used to assess symptoms, and to measure changes over time and in response to treatment. The component questions of the PROMIS instrument undergo rigorous testing in culturally and ethnically diverse populations, with a particular focus on the individual use of language to describe PROs. A wide variety of adult and pediatric (including parent proxy) PROMIS instruments are available for use in clinical trials, point-of-care visits, or large scale surveys.

3. Therapies

Broad areas of potential research directions include:

- Conducting studies on management of chronic symptoms, such as itch, fatigue, pain, and stress;

- Integrating patient-reported outcomes and clinical measures to support medical decision-making and improve quality of life for people with chronic conditions;
- Investigating placebo responses to pain and treatment, and the impact of catastrophizing and individual pain experiences in disease management and treatment response;
- Exploring integrative and complementary therapies, such as biofeedback, relaxation, mind-body interactions, cognitive behavioral therapy, and exercise;
- Investigating the role of non-pharmacological treatments and combined individual, group, and technology-based interventions for self-management and improvement of health-related behaviors; and
- Investigating use of behavioral interventions (e.g., diet, dietary supplements, various forms of exercise) to manage disease symptoms or prevent disease progression.

II. SKIN BIOLOGY AND DISEASES

NIAMS Skin Biology and Diseases programs fund basic, translational, and clinical research in skin, including a variety of both common and rare skin diseases. These programs include investigations of the molecular, cellular, and developmental biology of skin, as well as the study of skin as an immune, sensory, endocrine, and metabolic organ. Research on wound healing, autoimmunity, inflammation, heritable diseases, and birth defects is also included within this portfolio whose goal is to translate fundamental research findings into novel diagnostic tools, effective therapeutics, and efficient, cost-saving disease management.

Understanding skin biology in the context of whole-body physiology is a new horizon. As an integral part of the human body, skin function and skin diseases are influenced by both internal and external environments. Increasing evidence suggests that skin homeostasis is modulated by the immune, nervous, and endocrine systems, as well as by circadian rhythms and resident microbial flora. Studying interactions between skin and other organs is increasingly important for advancing knowledge of skin health and disease and thus calls for multidisciplinary collaborations to invigorate and enrich the skin research field.

A. Skin Biology and Diseases: Trans-discipline Basic Studies

Advances in basic research on skin biology have been the foundation for improving skin health over the past century. Basic research will continue to be the driving force for innovation in combating diseases that affect skin, hair, and nails and that include specific skin regions such as the scalp, and areas of skin with appendages.

1. Skin molecular and cell biology

Broad areas of potential research directions include:

- Investigating chromatin structure and epigenetic mechanisms;
- Studying transcriptional, co-transcriptional, and post-transcriptional regulatory mechanisms;
- Studying non-coding RNA regulatory networks;
- Studying the mechanisms of cell division, proliferation, and differentiation;
- Identifying novel mechanisms in cellular movement, sensing, intracellular transportation, and secretion;
- Developing new or improved technologies to isolate and characterize single cells and small populations of cells from skin;
- Investigating interactions between the skin and other organ systems, as well as systemic effects of perturbations in skin homeostasis; and
- Defining regulatory networks in gene regulation and cellular communication.

2. Stem cells

Skin function is developed and maintained by a variety of stem cells (e.g., keratinocyte stem cells, hair follicle stem cells, melanocyte stem cells, sebaceous gland stem cells, mesenchymal stem cells, etc.). Understanding skin stem cells is a key research area.

Broad areas of potential research directions include:

- Defining stem cell populations in skin, determining the regulatory mechanisms that control self-renewal and lineage commitment, and elucidating the role of these cells in skin development, homeostasis, and diseases;
- Defining the location, components, and properties of stem cell niches, and how these niches maintain stem cell populations;
- Defining stem cell developmental potential (pluripotency), progeny heterogeneity, and the possibility of inter-lineage conversion via dedifferentiation;
- Mapping cellular lineages in skin and determining how different cell types/subtypes interact with each other, and the importance of these interactions on development, homeostasis, and disease; and
- Exploring the use of induced pluripotent stem (iPS) cell technology as a tool of research and a modality of therapy.

3. Developmental biology

- Understanding the development of mammalian skin;

- Defining specific genes and regulatory pathways in the development of skin and its appendages, including use of cell type-specific knockouts and overexpression;
- Defining and understanding regulatory signals (cytokines, growth factors, morphogen gradients, etc.) that shape skin as an organ; and
- Elucidating interactions between components of dermis and epidermis during development.

B. Skin Biology and Diseases: Skin as a Barrier

The primary function of skin is to provide a physical barrier that is flexible, resilient to mechanical force, properly sealed, capable of blocking ultraviolet radiation, and with regional specializations to accommodate movement, pressure, and friction. The skin barrier is also biological, keeping microbial flora at appropriate levels and repelling their infiltration. Defects in skin barrier structure and function are a major cause of disease.

1. Keratinocytes (epidermis)

Keratinocytes are the principal cells that form the body's outer physical barrier. Keratinocytes also contribute to the immune and sensory functions of skin.

Broad areas of potential research directions include:

- Delineating the differentiation pathways of keratinocytes in vitro and in vivo, to improve understanding of skin diseases, to identify potential therapeutic targets, and to guide the transformation of iPS cells into differentiated keratinocytes;
- Investigating structure and function of protein complexes that maintain structural integrity of epidermis – such as desmosomes, hemidesmosomes, and cytoskeleton – and related genetic defects that contribute to pathogenesis of pachyonychia congenita, forms of epidermolysis bullosa, and other diseases;
- Exploring structure and function of the skin permeability barrier (the stratum corneum), and how it changes with skin aging and disease;
- Identifying targets for therapies to restore normal barrier function in disease and conditions such as premature birth;
- Determining how changes in the skin barrier in injured or diseased skin affect drug concentrations in skin during topical therapy;
- Studying epidermal function as a barrier to transported molecules to inform development of delivery methods for topical agents;
- Determining the role of circadian rhythms on barrier function; and
- Investigating the role of keratinocytes in skin immune and sensory functions.

2. Skin photobiology and melanocytes

Electromagnetic radiation, visible or invisible, has many effects on normal and pathological skin physiology. As a primary shield of this radiation, melanocytes possess unique properties to protect vital stem cells and subcutaneous tissues. Pathological conditions affecting melanocytes can lead to hyper- and hypopigmentation of skin that can significantly affect an individual's quality of life.

Broad areas of potential research directions include:

- Studying effects of electromagnetic radiation on skin biology (e.g., activation of melanin synthesis, vitamin D synthesis and immunosuppression);
- Investigating melanocyte lineage development (see also Stem cells);
- Investigating melanocyte proliferation, differentiation, and population heterogeneity;
- Studying pigment synthesis and transport pathways;
- Improving understanding of interactions of melanocytes with other cell types, especially with cells of the immune system that contribute to vitiligo;
- Exploring the role of melanocyte in overall skin photobiology;
- Identifying molecular and genetic differences between pre-neoplastic nevi and senescent nevi that do not develop into invasive melanomas; and
- Identifying genetic and molecular components of inherited pigmentation disorders such as oculocutaneous albinism.

3. Fibroblasts and extracellular matrix

Basement membrane and dermis provide much of the structural support and mechanical strength of the skin barrier. The role of extracellular matrix in regulating cytokine activity and cellular behavior has just begun to be appreciated. A major focus of research in this area is determining how fibrosis develops. Another important area is understanding inherited defects in extracellular matrix proteins, i.e., heritable connective tissue disorders (see also Genetics of Skin Diseases and Birth Defects.)

Broad areas of potential research directions include:

- Investigating the biology of normal fibroblasts and their many variations (e.g., trans-differentiation to myofibroblasts) during normal and diseased physiology (the latter may lead to excessive deposition of extracellular matrix, such as in sclerosis and fibrosis);
- Identifying and characterizing subpopulations of fibroblasts in dermis, including developmental origins, roles in skin homeostasis, and contributions to repair after injury;

- Defining dermal fibroblast diversity in different body sites, to understand cell types involved in skin diseases that preferentially affect distinct parts of the body (in conjunction with skin innervation patterns; also see Skin as a Sensory and Endocrine Organ);
- Elucidating interactions between epidermal and dermal components crucial for normal processes such as hair-follicle development and hair cycling, and define roles for these interactions in diseases;
- Researching the biology of adipocytes, including their functions in skin homeostasis, repair after injury, and disease;
- Studying mechanisms that control the normal assembly, interactions, and function of molecular components of the extracellular matrix (ECM) (e.g., collagens, fibrillins, matrix metalloproteinases);
- Studying regulatory function of the ECM (e.g., in cytokine bioavailability);
- Studying ECM-cell interactions (e.g., via integrin); and
- Understanding mechanisms of ECM-related diseases (e.g., scleroderma, Marfan syndrome, Ehlers-Danlos Syndrome, dystrophic and junctional epidermolysis bullosa, pseudoxanthoma elasticum).

4. Vasculature

Broad areas of potential research directions include:

- Expanding understanding of mechanisms controlling angiogenesis, lymphatic genesis, and structure and function of lymphatic/blood vessels in normal skin development;
- Investigating and understanding the cellular/molecular/genetic biology of skin vasculature that contributes to cutaneous vascular malformations or affects angiogenesis in chronic wounds, inflammatory, fibrotic and psoriatic diseases; and
- Understanding the cause of skin vasculature birth defects (e.g., hemangioma and port wine stain) and developing effective therapies.

5. Breach of the barrier

Barrier defects and wounds can lead to a variety of skin diseases. Barrier leakage can cause excessive loss of water and other small molecules or increased infiltration of environmental substances including microorganisms that lead to skin immune reactions. More severe disruption of the skin barrier triggers a wound-healing response, a complex process shaped during evolution to ensure rapid restoration of tissue integrity. This occurs through a coordinated response involving the actions of a large repertoire of cell types that perform multiple functions: covering a wound bed, fighting microbial infection,

and rebuilding tissue architecture. Wound healing studies are therefore inherently multidisciplinary.

Broad areas of potential research directions include:

- Studying the molecular basis of barrier leakages and their consequences;
- Studying the relationship between barrier defects and skin immune reactivity;
- Understanding how wound-healing begins and ends;
- Defining minimal injury at the molecular level that triggers wound healing;
- Understanding how injury is detected;
- Studying basic mechanisms of wound healing, such as stem cell activation, cell-identity change, cell migration, differentiation, ECM remodeling, angiogenesis, and inflammation control.;
- Studying the role of macrophages in wound healing, particularly the regulatory and coordinating function of these cells in orchestrating healing and tissue rebuilding;
- Studying the role of systemic/mesenchymal stem cells (e.g., bone marrow derived) in skin wound healing;
- Understanding interactions of multiple systems, factors, and pathways, such as interactions among components of epithelia; endothelia; mesenchymal, immune, and inflammatory cells; and connective tissue;
- Researching the milieu of slow-healing and chronic wounds to identify factors that impair healing (These include microbial populations, hypoxia, inflammatory cytokines, cellular dysregulation and other physical and chemical properties of a chronic wound);
- Developing animal models of chronic wounds that more closely mimic human responses, to investigate new experimental therapies;
- Defining molecular and genetic mechanisms that contribute to aberrant/exuberant wound healing that leads to fibrosis or scar/keloid formation (Fibrosis is invariably triggered by injury and thus intrinsically related to healing.);and
- Exploring the role of ECM remodeling in normal wound healing and diseases (e.g., chronic wounds, keloids), as well as effects of ectopic mineralization.

C. Skin Biology and Diseases: Skin as an Immune Organ

Skin is not only a major physical barrier but also a complex neuroimmune organ densely coated by microbial communities and populated by keratinocytes and resident immunocytes. In combination, these cells provide a robust immunological barrier to potential insults. In response to invading pathogens, groups of cells including microbial commensals, keratinocytes, and immunocytes, together neutralize invaders and subsequently restore skin homeostasis. Failure to restore skin homeostasis may lead to microbial dysbiosis and deregulated cutaneous innate and/or adaptive immunity, resulting in inflammatory and/or autoimmune skin diseases. An example of a recent discovery in this area is featured in the box "Understanding Atopic Dermatitis (AD)".

Understanding Atopic Dermatitis (AD): A recent study suggests that δ-toxin, a protein produced by *S. aureus,* promotes the allergic skin reaction observed in individuals with AD. Because activation of mast cells is known to play a role in AD, researchers tested the effects of *S. aureus* toxins on laboratory-grown mast cells They found that δ-toxin activates mast cells not only in the laboratory, but also when injected into mouse skin. Previous research demonstrated that the antibody, immunoglobulin-E, or IgE, also triggers the activation of mast cells in AD. The researchers investigated whether the δ-toxin and IgE use the same processes to trigger mast-cell activation. Although δ-toxin worked synergistically with IgE in the activation of mast cells, their results showed that the two molecules exert their effects via slightly different mechanisms. To determine whether δ-toxin promotes allergic skin disease, the researchers infected experimental mice that are susceptible to allergic skin disease with *S. aureus.* The mice developed AD-like lesions at the sites where the bacteria were applied. The δ-toxin produced by S. aureus and enriched in lesional skin of patients with AD was identified as a potent inducer of mast cells degranulation. In addition, δ-toxin has the ability to synergize with IgE in the activation of mast cells. This study helps to understand the mechanism by which a factor released by microbes collected in lesional skin of people with AD activates resident immune cells and exacerbates skin allergy in mice.

Reference:
Nakamura Y, et al. Nature. 2013. PMID: 24172897

1. Immunobiology of the skin

Keratinocytes screen their microenvironment continuously and respond rapidly to signals by expressing pro-inflammatory cytokines, chemokines, and antimicrobial peptides (AMPs). In addition, keratinocytes can initiate adaptive immunity by presenting foreign antigens to resident skin memory T cells and effector T cells. Multiple other

types of immunocytes, such as langerhans cells (that reside in epidermis and constantly sense the microbiome), dermal dendritic cells, macrophages, monocytes, eosinophils, mast cells, and innate lymphoid cells also screen the external microenvironment, epidermis, and/or dermis. Overall, these immunocytes key effectors of innate and adaptive skin immune responses against invading pathogens and/or tumors. Importantly, microbial commensals help the skin-based immune system to mature and release factors such as AMPs that antagonize pathogen invaders. Skin is also innervated, and researchers are investigating mechanisms by which skin's immune and nervous systems communicate. Findings focused on the regulatory role of microbial commensals, keratinocytes, and immunocytes – and their expressed factors, such as cytokines, chemokines, microbial and keratinocyte AMPs and neuropeptides – have opened new avenues to understand the immunobiology of healthy and diseased skin.

Broad areas of potential research directions include:

- Studying skin as an active immune organ, focusing on keratinocytes and immunocytes (such as resident memory $\alpha\beta$-T cells or $\gamma\delta$ T cells) that reside in and traffic through skin, as well as their receptors and soluble factors (Appropriate tools include animal models, human tissues, single-cell analyses, three-dimensional cultures, and real-time in vivo imaging technologies. Studies demonstrating the relevance of observations in mouse models to human disease are also needed.);
- Developing in vivo and in vitro models to define key regulatory signaling pathways activated in human keratinocytes and/or immunocytes by chemical insults, skin tumors, resident skin commensals, and/or invading pathogens using novel reagents and techniques (such as novel immune-profiling tools);
- Discovering new mechanisms by which keratinocytes and immunocytes interact and synergize (Characterize mechanisms by which skin immunocytes affect hair follicle biology.);
- Phenotyping the microbiome in healthy and lesional skin, and defining bidirectional molecular signals that skin microbial communities use to communicate with each other and with the cutaneous immune system;
- Defining how changes in the skin barrier affect microbial communities on the skin's surface and their access to the dermal compartment;
- Defining mechanisms by which resident microbial flora influence development and function of skin as an immune organ;
- Investigating host genetic factors that control establishment of the microbiota;
- Defining mechanisms by which resident microbiota of the gut, lung, oral cavity, and other mucosa affect skin's resident microbial communities, as well as how skin microbiota affects microbial communities in mucosal body sites;

- Understanding the molecular basis by which the cutaneous immune system and systemic immune system influence one another;
- Developing models to define the molecular basis by which the cutaneous immune system and the nervous system communicate in healthy and diseased skin;
- Understanding the molecular basis by which the cutaneous immune system and coagulation systems interact to regulate skin inflammation;
- Understanding how skin endocrine signals regulate skin immunobiology;
- Developing imaging and nanotechnology approaches to study skin structure trafficking in situ, and interactions of immune cells in skin;
- Analyzing influences of subcutaneous adipocytes and corresponding lipid metabolism in the control of skin immune functions;
- Developing in vivo models to define mechanisms by which the body's circadian clock regulates skin immunobiology and homeostasis; and
- Defining the role of the immune system in the initiation, development, and surveillance of skin cancer.

2. Inflammatory and immune skin diseases

Samples of skin are readily accessible, and skin is the primary target organ of many inflammatory and autoimmune diseases. These characteristics facilitate the implementation of systems biology approaches to skin disease research that defines functional signatures (e.g., activated cellular subsets; differentially regulated genomics; epigenomics, transcriptomics, and proteomics; antibody and receptor repertoires; signal transduction pathways; metabolomics; and the microbiome). Novel bioinformatics tools and infrastructure are needed to advance research on the mechanisms by which these functional signatures contribute together to pathogenesis in specific diseases.

GWAS and deep genome-wide sequencing studies are yielding important results for complex skin disorders, such as atopic dermatitis, psoriasis, alopecia areata, and vitiligo. Yet, the majority of genetic signals associated with psoriasis, for example, as well as other immune-mediated diseases, do not reside in known gene-coding regions. Efforts such as the NIH ENCODE (Encyclopedia of Coding DNA Elements) are generating data needed to accurately co-localize risk loci. On-going functional genomics studies are identifying key molecular and cellular pathways and are revealing important insights into disease mechanisms that may lead to new treatments.

a. Genetic and epigenetic studies of skin immune diseases

Research is needed to improve understanding of disease risk and pathogenic pathways that contribute to complex disease pathogenesis. Integration of information obtained from GWAS, deep genome-wide sequencing studies, ENCODE, chromatin structure

and epigenetic markers data and functional genomic studies will advance understanding of skin immune diseases.

Broad areas of potential research directions include:

- Integrating data from functional and mechanistic studies – for example proteomics, microbiomics, and metabolomics – with common and rare risk loci identified by genetic and genomic approaches to investigate the relationship between genotype and phenotype and to understand pathogenic mechanisms and disease progression;
- Using public data on functional elements of the human genome, available from the ENCODE Project, the NIH Roadmap Epigenomics Project, and other sources, to prioritize coding and non-coding disease risk variants and develop mechanistic hypotheses for follow-up functional studies (Generate similar data for the many cell types in skin and make these data broadly available.);
- Investigating how common and rare variants identified using genomics approaches contribute to disease pathogenesis through functional genetic studies in animal and in vitro model systems; and
- Studying roles of gene-environment interactions, epigenetics, non-coding regulatory DNA, chromatin interactions, and other modifiers of gene expression (e.g. microRNAs, lncRNAs) in disease pathogenesis.

b. Pathogenesis Studies

More research is needed to discover innate and/or adaptive cellular and molecular mechanisms that trigger and control inflammatory and autoimmune conditions such as pemphigus, pemphigoid, psoriasis, psoriasis arthritis, atopic dermatitis, alopecia areata, cicatricial alopecia, vitiligo, acne, rosacea, and others.

Broad areas of potential research directions include:

- Defining specific innate or adaptive signaling pathways that can be targeted to treat inflammatory and autoimmune skin diseases (Define shared and convergent innate or adaptive signaling pathways than can be targeted in more than one inflammatory and autoimmune skin disease.);
- Examining deep-sequencing results of antibody repertoires in pemphigus and pemphigoid and characterize autoantibody repertoires that define self and foreign antigens (Explore the mechanisms by which autoantibodies cause blistering of skin in immunobullous diseases, to inform development of drug therapies);
- Studying the role of the skin microbiome as a potential trigger and regulator for autoimmune and inflammatory diseases of skin;

- Assessing how the microbiome may serve as a biomarker to predict outcomes of skin diseases (Define the impact of dysbiosis on healthy immune function and its contribution to inflammatory and autoimmune disorders of skin);
- Investigating the role of the inflammasome and other modulators of inflammation in skin diseases;
- Investigating innate and adaptive signaling pathways that contribute to disease co-morbidities such as cardiovascular disease, metabolic syndrome, and diabetes;
- Using novel epidemiology methods to link skin diseases with systemic co-morbid conditions;
- Discovering triggers of inflammation and autoimmunity (Investigate single or shared mechanisms involved in the onset, development and progression of these diseases.);
- Characterizing altered lipid metabolomics and glycolysis pathways leading to inflammatory and autoimmune skin diseases;
- Investigating how efficacious drugs affect cellular metabolism; and
- Investigating mechanisms by which circadian rhythms affect immune-mediated skin diseases (Delineate immune mechanisms underlying the common symptom of itching.).

D. Skin Biology and Diseases: Skin as a Sensory and Endocrine Organ

Skin is the body's largest interface with its immediate external environment, and it is exposed to numerous physical, chemical, and biological stimuli. Thus, over time, skin has evolved into a sensory organ and an extension of the body's nervous and immune systems that interacts with, the external environment (see box "Understanding Chronic Itch"). Skin is also an endocrine organ – known as a site of hormone synthesis – and capable of communicating with the rest of the body via multiple endocrine pathways.

Research needs and opportunities related to itch were discussed in greater detail at a 2010 NIAMS roundtable discussion.

Broad areas of potential research directions include:

- Studying skin innervation;
- Defining sensory functions of resident skin cells (e.g., keratinocytes, Merkel cells, components of hair follicle);
- Studying mechanisms of itch and pain and defining their mediators in skin under both normal and pathological conditions;
- Studying mechanisms of touch and temperature sensation;

- Investigating interactions among skin sensations, i.e., itch, pain, touch, and temperature;
- Developing therapeutic methods to control itch and pain in disease conditions;
- Investigating the role of skin innervation in normal tissue and in pathological conditions such as inflammation and chronic wounds;
- Understanding skin's endocrine function;
- Investigating circadian regulation of skin physiology; and
- Understanding the mutual influence of psychology and skin physiology under normal and pathological conditions.

Understanding Chronic Itch: One emerging area of research into skin's sensory functions focuses on understanding the biological basis of chronic itch, a symptom associated with many skin diseases. Chronic itch can be difficult to treat and manage, which can cause severe deterioration of a person's quality of life. Although the underlying cellular and molecular mechanisms of itch are not well understood, a number of new studies have identified cells, molecules, and pathways involved in chronic itch and have developed new tools to study the condition. For example, NIAMS-funded researchers recently reported the development of an innovative mouse model of chronic itch. The researchers focused on BRAF, a molecule known to control the activity of sensory neurons – nerve cells that send skin sensations like pain – to the brain. The researchers expected that activating BRAF in mice would produce pain-related behaviors such as face-wiping. But surprisingly, mice with activated BRAF instead scratched themselves, a behavioral response to itch. The scientists then found that when BRAF is activated in pain-sensing nerve cells, the molecule can convert pain-sensing nerve cells into itch-sensing ones, producing more itch-sensing molecules and sending even stronger itch sensations to the brain. The findings suggest that BRAF is an important regulator of itch sensation and thus could be a target for developing new therapies.

For more information about recent advances in understanding chronic itch, see Investigating the Causes of Chronic Itch: New Advances Could Bring Relief.

E. Skin Biology and Diseases: Skin Appendages

Skin appendages, (e.g., hair, nail, sebaceous glands and sweat glands) provide many of the auxiliary functions of skin. Compared to the epidermis, these epithelia-derived mini-organs/tissues are understudied. One exception is hair/the hair follicle – a powerful model system for understanding tissue/organ development and regeneration.

Broad areas of potential research directions include:

- Studying development and maintenance of skin appendages;
- Identifying potential stem cells and their niches;
- Understanding function and regulation of stem cells in normal skin and in pathological conditions;
- Investigating the etiology of diseases related to skin appendages; and
- Understanding the regenerative potential and conditions of skin appendages.

F. Skin Biology and Diseases: Genetics of Skin Diseases and Birth Defects

Many, if not all, aspects of skin function are known to be affected by genetic mutations, producing a spectrum of clinical manifestations ranging from minor, cosmetic, and irritant, (deteriorating quality of life) to fatal. Genetic factors that affect skin conditions can be monogenic or polygenic, including sequence variations in protein-coding DNA as well as in noncoding regulatory regions that operate through genetic and epigenetic mechanisms. Researchers are employing a large repertoire of therapeutic modalities to combat heritable skin defects with known or unknown etiologies (also see Therapy Development).

Broad areas of potential research directions include:

- Discovering new genetic underpinnings of skin diseases;
- Discerning genetic and environmental contributions in skin birth defects;
- Understanding processes in which a genotype is translated into a phenotype;
- Defining modifier genes and the effect of genetic background on phenotype heterogeneity (e.g., disease risk/severity assessment);
- Identifying genes that contribute to defects in skin functions, both in common skin diseases such as atopic dermatitis, as well as in rare inherited disorders such as Marfan Syndrome in which studies of pathogenesis may inform understanding of common diseases;
- Defining and characterizing biochemical and cellular networks affected by mutations underlying skin diseases;
- Understanding mechanisms of spontaneous reversion of disease phenotype in some genetic diseases and exploring therapeutic potential of these processes;
- Building genetic and epigenetic databases relevant to skin biology and skin diseases;
- Conducting GWAS to discover co-morbidities of skin diseases and understand shared pathways;

- Applying high-throughput genomic and epigenomic technologies, combined with mathematical and bioinformatics methodologies, to elucidate regulatory networks involved in normal skin biology and in disease states;
- Investigating the function of noncoding RNAs, including microRNAs and long noncoding RNAs (lncRNAs), in skin development and diseases; and
- Studying the genetic basis of heritable defects of skin development, known collectively as ectodermal dysplasias, to provide insights into regulatory pathways that are critical for the development of skin and its appendages.

G. Skin Biology and Diseases: Regenerative Medicine

Regeneration mimics the embryonic process that shapes original tissue; therefore, it heals injury without scarring and functional deficits associated with repair, which relies on the use of substitute, or "makeshift," material to close a wound rapidly. Treatment of large-area acute skin wounds, such as extensive burns and trauma, requires participation of both processes, and a key research challenge is how to restore tissue function after a wound is closed. Regenerative medicine in skin involves research on developmental processes, epigenetics, the skin microenvironment, and engineering approaches to create temporary tissue substitutes or to modify wounds to facilitate healing and functional restoration. Regeneration research advances understanding of adult organ neogenesis, which helps fully restore tissue function, and it also includes development of engineered living skin that aims to mimic native skin.

1. Skin embryonic development

The concept and practice of regenerative medicine are firmly rooted in developmental biology. Knowledge of developmental biology principles related to skin provides important insights into tissue regeneration. Studies of hair follicle neogenesis have revealed that adult skin may possess more regenerative capacity than previously thought. (See also Developmental Biology).

Broad areas of potential research directions include:

- Applying principles of skin and skin-appendage development to regeneration of normal skin in vivo following injury; and
- Applying knowledge of skin and skin-appendage development to engineering of replacement skin in the laboratory.

2. Tissue neogenesis

Broad areas of potential research directions include:

- Understanding skin's regenerative potential;

- Defining conditions that induce adult neogenesis or hinder it;
- Discovering mammalian model systems that can regenerate skin and appendages, virtually restoring full function (such as the African spiny mouse);
- Developing methods for in vivo tracking of exogenous (e.g., transplanted) cells in regenerative medicine applications, to determine if they play a transient or permanent role; and
- Defining factors that allow exogenous cellular engraftment and investigating approaches to maintain transplanted cells' unique properties in vivo.

3. Engineered skin tissues

Broad areas of potential research directions include:

- Developing a new generation of skin equivalents that can better mimic natural skin functions (e.g., vasculatures, immune functions, pigmentation, innervations);
- Developing modular skin three-dimensional (3-D) models that can interact with other organ models to study integrated human physiology (e.g., as proposed in the NIH Common Fund's Integrated Microphysiological Systems initiative);
- Exploring use of iPS cells in engineered skin;
- Exploring use of natural ECM components as biomaterials that provide appropriate structural and mechanical properties for generating functional skin (Develop biomaterials and scaffolds that mimic or result in functionally superior ECM.); and
- Developing wound coverings for drug/growth factor delivery to promote healing and regeneration.

H. Skin Biology and Diseases: Technology and Instruments

The accessibility of skin as an organ provides unique opportunities for developing technology for real-time, in vivo, non-invasive means of observation and intervention.

Broad areas of potential research directions include:

- Developing intravital microscopy technologies that allow analyses of the behavior of cells in their native environment and in real time, and adapt these technologies to the study of human skin;
- Developing instruments to measure non-invasively physical, mechanical and chemical properties of skin;
- Developing tracers and reporters for cell tracking, lineage tracing, and for monitoring biochemical processes in skin; and
- Developing photo/light sensitive probes for manipulating cellular and biochemical events in vivo.

I. Skin Biology and Diseases: Model Systems

In biomedical research and therapeutic development, hypotheses and drugs must be evaluated in model systems. These can be living organisms or in silico (computer or mathematical) models.

1. Animal models

Genetically modified organisms and many naturally occurring genetic variants are powerful tools for skin research. Even so, finding suitable models to address specific questions in skin research remains challenging. One recurring issue is whether findings in mouse models can be directly translated into understanding human biology. Pigs are regarded as a better model than other animals for skin studies, primarily because pig skin more closely resembles that of humans than does the skin of other animals. Transplantation of human skin to a mouse, or reconstituting the human immune system in a mouse, may be useful for investigating some human skin diseases, however. Complex diseases are likely to be modeled with transgenic mammals, and some polygenic diseases (e.g., alopecia areata) have emerged spontaneously in mice and in other large animals, such as dogs and monkeys. Research in small vertebrates (fish), invertebrates (flies and worms), and other less evolved organisms can be advantageous because researchers can examine large numbers of these animals using high-throughput technologies.

Broad areas of potential research directions include:

- Developing animal models to study the role of specific genes and regulatory pathways on the development of skin and its appendages, as well as on skin homeostasis;
- Generating and validating animal models that mimic human skin diseases, including grafting of human skin onto mouse skin to examine molecular and cellular processes in a controlled experimental environment;
- Using new gene-editing technologies (e.g., CRISPR/Cas, TALENs) to create animal models of human heritable skin diseases for studies of disease pathogenesis and testing of new therapeutic agents;
- Exploring use of zebrafish, flies, and other genetically tractable model organisms for modeling skin diseases and mutations and for high-throughput genetic screening;
- Developing animal models to study the role of skin microbiota in skin health and disease;

- Generating animal models to investigate mechanisms of tissue damage by toxic industrial chemicals and chemical threat agents and for testing the efficacy of potential countermeasures;
- Conducting research using human skin transplants and patient-derived or genetically engineered human skin equivalents, as well as reconstitution of the human immune system; and
- Combining genetically engineered animal models and intravital imaging to study trafficking of cells (e.g., immune cells) in live skin and to visualize specific cell populations such as stem cell subpopulations and their progeny.

2. In vitro cell-based models

Cultured skin substitutes and other in vitro models of skin are in current use, particularly for toxicology screening.

Broad areas of potential research directions include:

- Developing 3D tissue models of normal human skin and of skin diseases;
- Using patient-derived iPS cells and gene-editing technologies to create disease models to study the roles of specific genes and pathways in disease pathogenesis, as well as to test therapeutic agents for personalized medicine approaches;
- Developing efficient, highly reproducible, and scalable protocols to produce differentiated skin cell types from iPS cells; characterizing these differentiated progeny using functional assays and genomic technologies; and comparing them to cells in vivo;
- Exploring direct reprogramming of adult somatic cells as an alternative strategy to generating skin cells for in vitro models and for cell-based therapies; and
- Developing in vitro models to study host-microbe interactions in skin.

3. In silico modeling

Systems biology is a research approach used to understand the network behavior of biological systems, to predict effects of perturbations on a system, or to develop novel ways to modulate a system's behavior. In systems biology modeling, conceptual and mathematical models are developed and trained by test data and then used to predict the behavior of real biological systems. To facilitate development of a successful systems model, it is critical to attain consensus on standards for collecting and reporting research results.

Broad areas of potential research directions include:

- Modeling regulatory networks of genes, proteins, and cells in skin;
- Encouraging collaboration among biologists and mathematicians to enable the use of systems biology approaches to model complex biological systems;
- Developing disease models (such as virtual patients) to inform clinical trial design and clinical practice; and
- Enhancing training in computational biology and bioinformatics.

J. Skin Biology and Diseases: Therapy Development

Knowledge of pathogenic pathways, as well as of basic skin biology, allows development of small-molecule and biologic therapies (e.g., antibodies) that target specific components of these pathways. Such approaches facilitate effective and systemic treatment with minimal side effects, which is desirable for widespread skin lesions. Because of the accessibility of skin, treating diseases of skin, hair, and nails – including diseases of the scalp and of skin appendages – need not be limited to chemical interventions, since physical methods have also been explored.

Needs and opportunities related to therapies for pediatric dermatologic disease were discussed in 2011 at a NIAMS roundtable.

Broad areas of potential research directions include:

- Translating gene-based discoveries into novel therapeutics;
- Exploiting drug repurposing for skin therapeutics;
- Discovering small molecular activators and inhibitors of cellular processes as potential therapeutic agents;
- Studying the pharmacogenomics of responders and non-responders to pharmacologic and biological interventions in skin diseases, toward directing therapies to appropriate subsets of patients; and
- Developing interventions that reverse, not merely delay, adverse changes that occur in aging skin.

1. Gene and cell-based therapy

Correcting defective genes may be possible to treat monogenic skin diseases such as epidermolysis bullosa (EB) simplex (see box, "Therapy Development for Epidermolysis Bullosa"), One possible approach would be to use CRISPR/Cas technology in combination with iPS cells, thus addressing the disorder's root cause.. Another approach, being tested for people with EB, is treatment with donor-derived bone marrow stem cells.

Therapy Development for Epidermolysis Bullosa: Multiple new treatments are under development for epidermolysis bullosa (EB), a family of genetic disorders that cause epidermal and mucosal fragility and blistering. Two recent studies in mouse models examined the efficacy of human recombinant type VII collagen (C7) for treatment of recessive dystrophic EB (RDEB), a severe form of EB caused by mutations in the C7 gene. In one study, recombinant C7 restored epidermal adherence when applied topically to wounds in RDEB mouse skin.[1] In contrast, no C7 could be detected when recombinant C7 was applied to intact RDEB skin, suggesting that topical application of C7 might be effective on existing wounds, but may not be useful for preventing new blisters. In a second study, recombinant C7 administered intravenously to RDEB mice migrated to unwounded RDEB skin and corrected the dermal-epidermal separation characteristic of RDEB, suggesting that intravenous administration of C7 might prevent new blisters and wounds.[2] In addition to these approaches that use topical and systemic treatment with recombinant protein, researchers also are testing autologous blood and bone marrow transplantation to treat RDEB. Early results suggest that transplanted donor cells travel to wounds, secrete normal C7, and improve clinical outcomes for patients. This offers hope that a similar strategy could be used to treat people with other inherited skin disorders.[3] NIAMS is also funding a phase I clinical trial in which RDEB patients are being treated with grafts from their own skin that have been genetically engineered to express C7 (NCT01263379). Collectively, although these results represent significant advances toward the goal of an effective therapy for EB, more work is needed to develop and test these treatments.

References:

[1] Wang X, et al. Mol Ther. 2013. PMID: 23670575
[2] Woodley DT, et al. J Invest Dermatol. 2013. PMID: 23321924
[3] Toler and Wagner. The Lancet. 2013. PMID: 24095195

Broad areas of potential research directions include:

- Developing in vivo and ex vivo gene therapies that target single-gene causal defects in skin diseases (e.g., various forms of EB);
- Developing systemic therapies for inherited skin diseases, e.g., bone marrow transplantation and protein replacement therapy;
- Investigating the use of small interfering RNAs to treat skin diseases by modulating expression of both normal and defective genes;
- Investigating effective in vivo molecular and cell delivery strategies to heal acute and chronic wounds;

- Developing ex vivo and in vivo gene-correction strategies to treat genetic skin diseases; and
- Exploring the therapeutic potential of various types of stem and progenitor cells, iPS cells, and embryonic stem cells to generate artificial bioengineered skin replacements for acute and chronic wounds and to repair or regenerate other tissues.

2. Cutaneous and transcutaneous drug delivery

Broad areas of potential research directions include:

- Exploring novel mechanisms of drug delivery to epidermis and dermis;
- Investigating topical delivery of small molecules and larger biomolecules, such as enzymes, monoclonal antibodies, and nucleic acids; and
- Developing transcutaneous drug delivery strategies for efficient and controlled administration of biological therapeutic agents for systemic diseases.

3. Physical therapies

Broad areas of potential research directions include:

- Discovering, developing, and refining physical methods for diagnosing and treating skin diseases.

K. Skin Biology and Diseases: Clinical Research

Skin diseases, which frequently compromise quality of life, are not always seen as important research targets relative to illnesses with greater mortality and morbidity. However, the impact of skin disease on people's lives is significant. Furthermore, some skin diseases are accompanied by systemic effects and co-morbidities.

1. Clinical trials and outcomes measures

A clinical trial is one of the most challenging steps for translating laboratory discoveries to improved health for people. A clinical trial should be based on the results of solid pre-clinical studies, a clearly-defined patient cohort, an efficient recruitment infrastructure, a robust statistical design, and unambiguous outcome measures. Combination therapies, evidence-based comparison of treatments, and cost-effectiveness are critical topics for future research.

Broad areas of potential research directions include:

- Developing clinical biomarkers that predict disease progression and treatment outcomes reliably and can be used as surrogate endpoints in clinical trials;
- Creating resources required to move promising biomarkers from bench to clinic using state-of-the-art statistical, analytical, and computational methods;
- Developing and validating new outcomes instruments that better measure disease severity than current instruments and that provide uniform descriptions and data that are comparable across studies;
- Developing instruments that assess disease impact on quality of life for people and their families;
- Developing methods to collect patient reported outcomes (PROs) and incorporating PROs in clinical studies/trials;
- Exploring alternative designs of clinical trials for rare skin diseases in which cohort sizes may be very small;
- Conducting clinical trials in pediatric populations to determine safety, dosing, and efficacy of drugs approved for use in adults – with the ultimate goal of improving therapeutic options for children;
- Establishing novel disease-outcome measures and defining novel signatures of autoimmunity and inflammation onset and progression;
- Exploring alternative therapeutic applications of existing drugs for autoimmune and inflammatory conditions, comparing their mechanisms of action and efficacies with current therapies, and long term safety follow-up; and
- Exploring safety and efficacy of peptides and non-coding RNA-based therapy.

2. Epidemiology and health services research

The incidence and morbidity of skin diseases are important subjects for epidemiological research. Optimal distribution of health services for skin diseases highlights the relevance of treating illnesses with low mortality but significant physical and quality-of-life effects.

Broad areas of potential research directions include:

- Combining analysis of the natural history of disease with population-based epidemiological studies to determine disease prevalence;
- Developing new measures to assess the burden of skin diseases on specific populations;

- Facilitating observational and epidemiological studies of skin disease co-morbidities and gene-environment interactions that may trigger or exacerbate skin diseases;
- Investigating skin disease co-morbidities as a potential impact on health disparities;
- Investigating whether therapeutic skin disease intervention(s) affect risk for developing co-morbidities;
- Examining the cost-effectiveness and comparative effectiveness of therapies and combination-therapy approaches for skin disease treatment; developing infrastructure needed to conduct these studies; and
- Researching effects of patient-health care system interactions on disease outcomes, considering in particular minority and underserved populations.

3. Prevention studies

Broad areas of potential research directions include:

- Developing strategies to identify, assess, and reduce disease risk factors;
- Conducting early intervention trials, to prevent onset or progression of disease; and
- Exploring use of personal communication devices and the Internet as tools for education, monitoring, and intervention.

L. Skin Biology and Diseases: Behavioral and Biopsychosocial Research

Environmental triggers of many skin diseases, such as ultraviolet radiation from the sun for skin cancer, are modifiable risk factors. These risk factors underscore the role of behavior as a contributor to health and disease, and they provide an opportunity for prevention and intervention through behavior modification. People disfigured by skin diseases are frequently affected by psychosocial problems due to social stigmas.

Broad areas of potential research directions include:

- Exploring measures, including behavioral modification and protective strategies, to prevent skin exposure to ultraviolet radiation that causes cancer and accelerated skin aging;
- Conducting behavioral and psychobiology studies with potential to improve understanding of skin disease mechanisms;
- Using social, commercial, economic, and cognitive data (“Big Data”) to understand correlations between behavior and skin diseases;

- Studying mechanisms by which stress affects skin disease progression and wound healing, and how stress management techniques and interventions impact disease outcomes and treatment response;
- Determining how the placebo effect influences disease outcome and treatment response;
- Investigating management of chronic symptoms, such as itching and pain, as well as ways to minimize effects of these symptoms on sleep and overall quality of life;
- Using biopsychosocial approaches to understand how gender and/or ethnic and/or socioeconomic differences influence clinical disease outcomes, symptom perception and management, and individuals' interactions with the health-care system; and
- Incorporating use of patient-reported outcomes instruments into clinical trials on skin diseases, to assess effects of therapy on disease-specific quality of life.

III. BONE BIOLOGY AND DISEASES

NIAMS bone biology and diseases programs fund a broad spectrum of basic, translational, and clinical research on buildup and breakdown of bone. Acquisition and preservation of adequate bone mass, as well as maintenance of architectural and material qualities that confer bone strength, are crucial for protection against fracture. Osteoporosis, or low bone mass, increases risk of fracture with its attendant morbidity and reduced quality of life. In the United States today, more than 40 million people either already have osteoporosis or are at high risk due to low bone mass. Because osteoporosis is common among older people – particularly in women past menopause – prevention, diagnosis, and treatment of osteoporosis will continue to have major public health implications as the U.S. population ages. This goal is reflected in Healthy People 2020 – the Nation's public health agenda.

NIAMS supports studies on the control of bone remodeling; bone formation, bone resorption, and mineralization; as well as effects of hormones, growth factors, and cytokines on bone cells. The Institute oversees several large epidemiologic cohorts that characterize the natural history of osteoporosis and identify genetic and environmental risk factors that contribute to fracture. NIAMS bone biology and diseases programs also support research on causes, pathophysiology, and treatment of less common bone diseases, such as osteogenesis imperfecta and Paget's disease of bone, as well as on a wide range of developmental disorders of the skeleton, many of which are genetic in origin.

A. Bone Biology and Diseases: Biology and Physiology of Bone

1. Molecular and cellular mechanisms in bone

Key processes in bone remodeling are formation of new bone by cells called osteoblasts, and breakdown, or resorption, of old or damaged bone by cells called osteoclasts. In a healthy adult skeleton, these processes are balanced via the overall process of bone remodeling. Osteocytes, fully mature osteoblasts embedded in mineralized bone, have emerged as a crucial population of cells for controlling bone physiology. There is also increasing interest in the function of lining cells on the surface of bone with regard to their characterization and role in normal physiology and pathologic states. Disproportionate resorption compared to formation results in bone loss, which can increase risk of fracture. Understanding mechanisms that regulate functions of osteoblasts, osteoclasts, and osteocytes – and hence influence bone resorption or bone formation – could yield new therapeutic targets. An ability to manipulate such processes could also be essential for tissue-engineering efforts using bone-forming cells.

Broad areas of potential research directions include:

a. Anabolic mechanisms: new bone formation by osteoblasts

- Characterizing biochemical pathways that control proliferation of osteoprogenitor cells;
- Defining early and intermediate cell types in the differentiation of progenitors to mature bone-forming osteoblasts and osteocytes, and identifying factors that control progression through cellular lineages; and
- Elucidating mechanisms that control osteoblast activity and determine a cell's functional lifetime.

b. Resorption of bone by osteoclasts, leading to bone loss

- Characterizing biochemical pathways that control differentiation of osteoclasts from progenitor cells within the monocyte/macrophage lineage;
- Defining factors that control maturation of progenitor cells into active multi-nucleated osteoclasts; and
- Elucidating biochemical pathways that control osteoclast activity and functional lifetime of cells.

c. Mineralization of the bone matrix

- Defining mechanisms that initiate and control deposition of calcium phosphate crystals in the collagen matrix of bone;
- Elucidating factors that control bone mineralization in, and determining effects of, varying degrees of mineralization on bone's structural, functional, and mechanical properties; and
- Exploring causes of pathological calcification of soft tissues and exploring measures to prevent or reverse inappropriate mineralization.

d. Cell-matrix interactions in bone

- Characterizing specific interactions between osteoblasts, osteoclasts, and components of the extracellular matrix of bone that influence cell differentiation or activity;
- Determining interactions between osteocytes and bone matrix to help explain processes underlying embedding of cells in mineralized matrix formation and maintenance of the osteocyte network; and
- Identifying signaling pathways activated by cell-matrix interactions in bone.

e. Cross-talk between different bone cell types

- Identifying molecules produced in one bone cell type that influence another, including those that may be transported in exosomes (e.g., micro-RNAs);
- Elucidating sites where molecules with effects on bone cells are produced;
- Investigating effects of signaling molecules originating in other bone cell types on target cells, including mechanisms mediating coupling of bone formation with bone resorption; and
- Defining mechanisms that control osteocyte differentiation, including formation of osteocyte dendritic processes and the lacunar-canalicular system.

f. Mechanisms of fracture repair

- Defining cell types and biochemical pathways involved in recruitment of osteoprogenitor cells to fracture sites;
- Elucidating processes that lead to callus formation and remodeling of new bone, including the roles of loading, inflammation, and vascularization; and
- Identifying and characterizing factors leading to fracture non-unions (i.e., fractures that fail to heal).

g. Response of bone to mechanical loading

- Characterizing cell populations that mediate the anabolic response of bone to loading;
- Defining the role of the osteocyte network in mechanosensation and the response to loading;
- Determining the resorptive response of bone to conditions of unloading, such as microgravity and disuse; and
- Elucidating biochemical signals activated when bone cells are exposed to specific mechanical stimuli that may arise in bone under different loading conditions.

2. Integrated physiology and pathophysiology of bone

Over the past five years, researchers have made considerable progress in understanding connections between bone physiology and the broader network of biologic processes involving many different organs and tissues. For example, muscle function and muscle mass influence fracture risk, and energy metabolism (in which bone plays a role) affects muscle mass. In addition, interactions among conditions associated with aging, musculoskeletal function, and bone mass are still inadequately understood. Progress has been made in describing how diabetes, lipid metabolism, and inflammation affect the musculoskeletal system, but a more integrated approach is needed.

Scientists are now poised to make additional discoveries that will help to explain the connection between the skeleton and the nervous system, other mesenchymal tissues (e.g., fat, muscle, cartilage), the immune system, digestion and nutrition (including the role of the microbiome), and energy metabolism. Bone can be either a target or a regulator, and it likely performs both roles as it interacts with various systems in development, aging, and disease. Bone itself and the events contributing to bone health are connected with other biologic processes; many drugs for conditions apparently unrelated to bone may have unanticipated effects on the skeleton, and bone-building drugs may have unanticipated effects on other tissues within and outside of the musculoskeletal system (see box, "Anabolic Therapies and Strategies to Regenerate Bone and Other Musculoskeletal Tissues").

To fully appreciate interactions among organ systems, bone researchers should form interdisciplinary teams with scientists who specialize in other organ systems and metabolic pathways, and they should consider not only bone, but also other organs and systems that associate with bone as an integrated unit.

Anabolic Therapies and Strategies to Regenerate Bone and Other Musculoskeletal Tissues: Activating anabolic pathways in bone, cartilage, and muscle holds considerable potential for yielding new therapeutic approaches for diseases relating to the musculoskeletal system as a whole or to its individual components. In bone, for example, recent research efforts have led to the identification of potential new treatment targets with powerful anabolic bone-forming effects. These include the Wnt[1] signaling antagonists sclerostin and DKK-1[2] agents that regulate or mimic PTH[3] action (e.g., PTHrP,[4] and calcilytic drugs aimed at the calcium sensing receptor); and components of the BMP/TGFβ[5] pathways.

Many of these molecular targets and pathways are shared among different musculoskeletal tissues and play prominent roles in many other cells. General knowledge is improving regarding links between bone metabolism, energy metabolism, and the central nervous system. Recent advances have led to a recognition that, in order to fully explore the potential and consequences of anabolic therapies, bone, cartilage, and muscle must be viewed as components of a network that includes not only other tissues of the musculoskeletal system, but also other organs and systems currently considered to be outside the musculoskeletal system.

Taking a system-wide view would represent a paradigm shift, since bone, cartilage, and muscle research communities have traditionally focused on single tissues of interest. Get more information about research needs and opportunities regarding anabolic therapies and strategies to regenerate the musculoskeletal system.

[1] Wnt = wingless-type mouse mammary tumor virus (MMTV) integration site family [2] dickkopf-related protein

[3] PTH = parathyroid hormone

[4] PTHrP = parathyroid hormone-related protein

[5] BMP = bone morphogenetic protein; TGFβ = transforming growth factor beta

Broad areas of potential research directions include:

a. Bone physiology and energy metabolism

- Characterizing factors that determine whether mesenchymal progenitor cells differentiate into osteoblasts or adipocytes;
- Determining the influence of body mass and body composition on bone homeostasis and bone strength (Such research could include studies to explain the relationship between bone physiology and the regulation of distinct fat depots (e.g., subcutaneous, visceral, and marrow fat)); and

- Elucidating the relationship between bone physiology, obesity, and glucose metabolism.

b. Bone and the nervous system

- Determining the influence of the nervous system on bone physiology, including effects of central nervous system signaling and the influence of circadian rhythms and
- Exploring roles of neurotransmitters and neuropeptides in bone.

c. Bone and the hematopoietic and immune systems

- Clarifying the importance of interactions between bone cells and cells of the hematopoietic and innate and adaptive immune systems, including components of bone marrow that influence bone physiology and bone remodeling;
- Defining functions of regulatory molecules that may affect both bone physiology and immune system development and function; and
- Examining mechanisms underlying bone destruction during inflammation and autoimmunity.

d. Bone and the vascular system

- Determining the relationship between angiogenesis (the formation of new blood vessels) and the processes of bone growth and remodeling and
- Exploring possible parallels and interactions between bone mineralization and the vascular calcification that occurs in cardiovascular disease.

e. Bone and cancer

- Elucidating mechanisms that underlie skeletal morbidity associated with malignancy, such as pathological bone destruction and formation and
- Exploring interactions between cancer cells and bone cells that mediate bone metastasis.

f. Bone as a component of joints

- Characterizing the interface and crosstalk between bone and cartilage in articular joints, including the notion that signals originating in bone may contribute to osteoarthritis;
- Defining mechanisms that lead to pathological bone formation in joints, such as osteophytes (bone spurs) or spinal stenosis; and

- Elucidating structure and function of interfaces between bone, ligaments, and tendons.

g. Bone and muscle

- Describing molecular and cellular communication pathways between bone and muscle, such as endocrine factors, neural influences, and exosomes;
- Determining roles of bone and muscle in the broad benefits of physical activity, including responses to mechanical stimuli and interaction with energy metabolism;
- Exploring possible synergies among therapeutic approaches that could yield improvements in both bone and muscle health and function; and
- Identifying differences and parallels in injured bone and muscle healing, including the origins of progenitor cells contributing to tissue regeneration.

3. Genetics and genomics of bone mass and fracture risk

Heredity influences many aspects of skeletal physiology, including age-associated changes. Although genetic influences on the skeleton are complex, reflecting contributions of many different genes, technological advances open a door to unprecedented understanding of individual risk for disease, as well as for personalized approaches to treatment. In recent years, high-throughput genotyping and sequencing technologies have been employed to analyze many clinical cohorts, largely substantiating the potential of genomic science to illuminate questions in skeletal biology and health. However, much of the heritability of skeletal traits such as bone mass and fracture risk remains to be identified. In addition, causal variants underlying disease associations, as well as the actual biochemical processes influenced by those variants, is still unknown in most cases. Filling in these gaps will require an integrated analytical approach, incorporating multiple data types to reveal functional aspects of the genome in humans and in animal models.

Broad areas of potential research directions include:

a. Functional genomics of skeletal tissues and cell types

- Acquiring and making broadly available, data reflecting the functional state of the genome (e.g., transcriptional activity, epigenetic characteristics) in cells of bone and cartilage;
- Identifying causal variants and molecular mechanisms accounting for genetic associations with skeletal traits; and

- Integrating insights from animal models, such as genetically modified mice and diverse inbred mouse strains, with human data to assign functional significance to specific gene variants.

b. Translating genomic insights into improved skeletal health

- Continuing to define genetic differences that underlie variation in bone formation, maintenance, and turnover;
- Characterizing genetic influences in humans that underlie ethnic and racial differences in bone mass, fracture risk, and fracture repair;
- Exploring how environmental exposures and aging interact with genetics; and
- Identifying genetic markers that predict drug response.

B. Bone Biology and Diseases: Developmental Biology and Stem Cells

1. Skeletal development

Bone shaping and growth during infancy and childhood are important for adult skeletal health. Increased research into processes by which bones originate in the embryo and grow during skeletal maturation promises to illuminate causes and potential treatments of developmental disorders in humans. This knowledge may also lead to more effective methods for enhancing repair and regeneration of bone damaged by disease or trauma.

Broad areas of potential research directions include:

a. Early skeletal formation and growth

- Elucidating mechanisms that establish bone location and shape during embryonic development;
- Identifying and exploring mechanisms that control the cartilage-to-bone transition during endochondral ossification, including chondrocyte hypertrophy and apoptosis, mineralization, and the role of vascular ingrowth; and
- Exploring environmental impacts on bone during growth and development.

b. Disorders of skeletal development

- Defining causal factors underlying skeletal development disorders such as the osteochondrodysplasias (Such research would expand knowledge on the roles of specific genetic mutations.) and
- Investigating biological mechanisms that underlie effects of mutations linked to skeletal development disorders, as well as cellular and molecular consequences of these genetic changes on developmental processes.

2. Stem cells

Bone cells arise from the differentiation of less specialized progenitor or stem cells, which can produce several different types of cells in response to various biochemical signals. Understanding these cells and the signals that guide them could improve tissue engineering and regenerative medicine approaches. Stem cells are also important targets of gene-based therapy strategies for genetic diseases of bone.

Broad areas of potential research directions include:

a. Mesenchymal progenitor cells

- Defining mesenchymal cell lineages to identify multi-potential precursors (adult stem cells) with osteogenic potential; exploring the role of tissue origin (e.g., marrow, adipose or periosteum) on differentiation potential;
- Developing cell lineage markers to identify stages of osteogenic and chondrogenic differentiation; and
- Investigating effects of regulatory factors, such as growth factors and bone morphogenetic proteins, on proliferation and differentiation of progenitor cells.

b. Embryonic and pluripotent stem cells

- Examining properties of animal and human embryonic stem cells with respect to osteogenic differentiation (Such research might include responses to specific growth factors and other regulatory molecules.) and
- Exploring the potential of iPS cells for differentiation along the osteogenic pathway (Studies could include investigating differences between induced and embryonically derived stem cells and effects of different strategies for inducing pluripotency.).

C. Bone Biology and Diseases: Imaging and Biomarkers of Bone Quality and Fracture Risk

Simple assessments of bone mass or bone mineral content fail to take into account large contributions of bone geometry, microarchitecture, and material properties that affect the ultimate mechanical performance of bone. Dual energy x-ray absorptiometry, the standard clinical measurement of bone density, is widely available and economical, but it gives only a rough estimate of bone quality and fracture risk. Understanding how architectural, material, and biochemical factors contribute to bone strength – and developing better methods of assessing these factors in the clinic – could lead to improved fracture risk prediction and treatment response monitoring.

Broad areas of potential research directions include:

1. Non-invasive measures of bone quality and fracture risk

- Analyzing architectural and material factors that influence mechanical performance of bone by directly studying specimens and by conducting modeling and engineering analyses;
- Developing and validating non-invasive measures of bone quality (such as those based on magnetic resonance, computed tomography, and ultrasound), and algorithms that could improve the clinical assessment of fracture risk (Such measures would also provide early indications of treatment effectiveness.); and
- Developing non-invasive tools that enable assessment of essential musculoskeletal functions, including biomechanical aspects of bone and muscle function.

2. Outcome measures and surrogate markers

- Identifying biochemical markers of bone strength and fracture risk that can be measured in easily obtainable biomaterials such as serum or urine;
- Investigating the utility of exosomes as bearers of tissue-specific biomarkers; and
- Testing candidate biomarkers in well-characterized clinical cohorts for which bone mass, bone quality, and fracture risk can be assessed independently.

D. Bone Biology and Diseases: Preclinical and Translational Research

Healthy and productive interactions between laboratory and clinical researchers are essential for translating basic discoveries into new drugs, treatments, and diagnostics. These relationships also foster environments in which clinical observations can prompt cellular and molecular studies that characterize a disease mechanism – leading to new biological insights as they advance the development of novel therapeutic agents.

Broad areas of potential research directions include:

1. Pathobiological mechanisms

- Characterizing molecular and cellular mechanisms underlying bone loss in common conditions such as sex-hormone deficiency, vitamin D insufficiency, chronic inflammation, and steroid drug treatment;
- Defining biological mechanisms underlying pathology in rare bone diseases, such as osteogenesis imperfecta and Paget's disease of bone and applying knowledge of potential therapeutic targets to develop and test new interventions for rare bone diseases;
- Investigating mechanisms of increased bone loss and fracture risk due to diseases of other organs and systems (such as HIV infection and diabetes) or

due to inactivity or unloading that accompanies many painful, debilitating musculoskeletal disorders;
- Examining biological processes that contribute to bone loss surrounding orthopaedic implants and developing bone-preserving strategies for implant recipients;
- Examining risk factors and mechanisms by which people taking bisphosphonate drugs develop atypical femoral fractures; and
- Developing pre-clinical animal models that represent more accurately initiation and progression of bone disease in humans.

2. Therapeutic mechanisms

- Defining biological mechanisms underlying effects, including side effects such as atypical femoral fractures, of widely used medications such as drugs prescribed to prevent or reverse bone loss;
- Examining why some therapeutic agents become less effective with long-term use;
- Exploring opportunities for discovery of newly identified molecular targets for new drug treatments;
- Exploring use of multi-modality therapeutic approaches to treat osteoporosis.
- Determining bone effects of drugs prescribed for diseases of other tissues and systems, since these drugs may have an impact on bone quality or fracture risk; and
- Translating knowledge about mechanobiology and bone response to loading into strategies for promoting fracture healing and bone defect repair.

3. Gene-based therapies

- Developing methods for recovery and re-introduction of cells in the marrow stromal/osteoblast lineage and exploring the potential of embryonic and iPS cells as mediators of gene-based therapies;
- Discovering innovative ways to use genetic modification of cells to correct genetic defects or to manipulate gene expression for therapeutic purposes; and
- Establishing gene-inactivation methods using various strategies such as viral vectors, small interfering RNAs, and genome-editing.

E. Bone Biology and Diseases: Clinical Research

1. Personalized medicine and clinical trials

Characterization of disease mechanisms in the context of clinical studies may enable researchers and health-care providers to distinguish between disease subtypes that produce similar endpoints (e.g., fracture). Furthermore, improved understanding of individual genetic variation is expected to lead to better prediction of drug response. The compendium of NIAMS-funded published research includes several studies that researchers could mine for information about variations in disease manifestation and treatment response. Research opportunities related to disparities in fracture risk and outcomes are described in the box "Eliminating Disparities in Fragility Fracture Incidence and Outcomes among Racial and Ethnic Groups."

In addition to examples identified under Imaging and Biomarkers, above, broad areas of potential research directions include:

a. Clinical trials

- Developing new therapies to prevent fractures associated with osteoporosis and related conditions;
- Assessing the potential of combining therapeutic agents to achieve additive or synergistic treatment benefits;
- Improving adherence to clinical protocols by developing and testing less-burdensome dosing regimens or routes of administration and exploring approaches that reduce drug side effects;
- Comparing the effectiveness of different therapeutic approaches; and
- Developing and validating novel outcome measures and surrogate markers that could be used to improve clinical trial efficiency.

b. Personalized medicine

- Developing improved predictors of fracture risk reflecting the contributions of an individual's environment, microbiomes, diet, lifestyle, and medical history;
- Exploring co-morbidity of bone diseases with other health problems and examining possible interactions between bone-active drugs and medications prescribed for other conditions;
- Examining variability in treatment response and determining mechanisms to explain disparate responses (e.g., why some patients are refractory to certain treatments, and why some develop serious side effects); and
- Investigating effects of genetic variation on treatment response.

Eliminating Disparities in Fragility Fracture Incidence and Outcomes among Racial and Ethnic Groups: A person's ethnicity and race, like his or her sex, influences the likelihood that he or she will develop osteoporosis and suffer fragility fractures of the hip, spine, and wrist. African ancestry is generally seen as protective against fracture, relative to European and Asian ancestry. However, bone health disparities as a whole are complex across groups. Although the overall incidence of hip fractures decreased between 1995 and 2006 for men and women,[1] additional work suggests that this decline is predominantly seen in whites.[2]

African American women are more likely than white women to die after hip fracture, and they are less likely to be able to walk independently upon hospital discharge.[3] This may be attributed largely to the fact that these women tend to be older when they suffer a hip fracture. African American women also suffer from more comorbidities that could affect recovery. The emerging biological links between bone, energy metabolism, and kidney function suggest that much can be learned from examining interactions in populations where comorbidities such as diabetes, obesity, and chronic kidney disease are most prevalent. The connection between race/ethnicity and changes in bone density, quality, and fracture risk over time also suggests areas of molecular diversity ripe for exploration.[4]

In addition to variations due to differences in genetic backgrounds, a range of environmental exposures, social and cultural issues, and access to and delivery of health care are likely involved. The changing demographics of the United States afford numerous opportunities for researchers to explore biologic and non-biologic causes of well-documented disparities related to fragility fractures, as well as to test strategies to ensure that all Americans benefit equally from efforts to improve bone health.

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[2] Wright NC, et al. J Bone Miner Res. 2012. PMID: 22692958
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2. Disease prevention and health promotion

NIAMS recognizes the importance of maintaining wellness in healthy populations and enhancing the well-being of individuals with bone disorders or diseases. Because motivating behavior change at a population level is an issue facing many NIH components, it may be possible to integrate research on bone-health messages with other health promotion programs that include diet and exercise components. Social

science approaches should be incorporated, where appropriate, into proposed research strategies.

Broad areas of potential research directions include:

a. Nutrition

- Defining the impact of nutritional status (e.g., vitamin D levels, protein intake) on bone health and fracture risk and
- Developing and testing strategies to promote bone health by improving nutritional status on a population level.

b. Environmental and behavioral interventions

- Developing and implementing cost-effective strategies to promote healthy bone formation during infancy and childhood;
- Examining the impact of physical activity levels on bone health and fracture risk and developing and testing strategies to promote bone health through exercise and physical rehabilitation programs; and
- Exploring effects of environmental factors, such as smoking and environmental toxins, on skeletal health.

IV. MUSCULOSKELETAL BIOLOGY AND DISEASES

NIAMS musculoskeletal biology and diseases programs fund a broad spectrum of basic, translational, and clinical research centered on the interplay between the body's muscles, bones, and connective tissues. These programs include research on the biology, structure, and function of joints and surrounding tissues and applying this knowledge to a variety of diseases and conditions, including osteoarthritis (OA). Other programs in this area fund tissue engineering and regenerative medicine to facilitate repair of damage caused by trauma to otherwise healthy tissue; imaging to improve diagnosis and treatment of bone and joint disorders; and clinical research toward the treatment and prevention of acute and chronic bone and joint injuries and orthopaedic conditions. Specific chapters within this Plan address basic, translational, and clinical research interests about bone, muscle, or rheumatic diseases.

Many conditions addressed by the NIAMS musculoskeletal biology and diseases research portfolio are those that become more prevalent and problematic with age. Americans over 65 years of age are the fastest growing segment of the U.S. population. This shift in the country's demographics emphasizes the need for prevention and treatment strategies for diseases and conditions that affect joints and other musculoskeletal tissues. Investments in basic biology, combined with burgeoning

opportunities in fields such as genetics/genomics and stem cells, will result in new opportunities for treatments that will ultimately improve clinical outcomes.

A. Musculoskeletal Biology and Diseases: Biology, Structure, and Function

1. Molecular and cellular biology of musculoskeletal tissues

A complex series of biochemical pathways and cellular interactions underlie the physiology of healthy, damaged, and diseased musculoskeletal tissues. Understanding the process by which a multicellular organism develops from its early, immature form into a fully mature form may deepen knowledge of disease mechanisms, regeneration strategies, therapeutic targets, and treatment design. Likewise, understanding the behavior of mature cells in their own environment is critical for developing cell-based strategies to repair or regenerate musculoskeletal tissues. Insights into how biological, chemical, and mechanical conditions affect cell behavior, as well as that of the microenvironment and the tissues from which those cells originate, would facilitate progress in this area.

Broad areas of potential research directions include:

a. Development, maintenance, and degeneration

- Characterizing molecules and signaling pathways that control cellular activities (e.g., stem cell renewal, pluripotency, and differentiation) essential for development and maintenance of musculoskeletal tissues;
- Elucidating factors that control critical regulatory and signaling proteins specific to development of joint tissues (e.g., articular cartilage, growth plate, meniscus, ligament, tendon, and intervertebral disc) and development of tissue interfaces;
- Elucidating the role of mechanical factors on cell signaling in development of musculoskeletal tissues and in disease;
- Investigating the role of specific cell populations (e.g., tendon and meniscus progenitor cells, synoviocytes) in tissue development and repair;
- Describing how cells interact with their local and systemic environments to establish and maintain functional musculoskeletal tissues;
- Examining influences of various connective tissue components during normal joint maintenance and repair or during joint deterioration caused by disease; and
- Investigating whether biological activities leading to joint degeneration originate in the bone, interfacial tissues, ligaments, menisci, or synovia.

i. Articular cartilage and chondrocyte biology

- Characterizing interactions between cartilage matrix proteins and determining how mutations in individual cartilage matrix proteins affect chondrocyte behaviors and overall tissue structure and function;
- Elucidating factors that contribute to chondrocyte cell death under normal or pathologic conditions;
- Identifying features of the articular chondrocyte that distinguish it from other forms of cartilage;
- Investigating structure and function of the bone-cartilage interface; and
- Studying the role of mechanical stimuli on the formation, maintenance, and destruction of extracellular matrices.

ii. Tendons, ligaments, and menisci

- Assessing effects of mechanical loading on the structural organization of menisci, tendons, and ligaments;
- Exploring the structural organization and biogenesis of tendons, ligaments, and menisci, and their interfaces with muscle and bone (Mechanisms underlying enthesis formation may be relevant to processes involved in joint degeneration.);
- Identifying differences that contribute to improved healing of lateral meniscal damage or that inhibit repair of damage to the medial side; and
- Studying mechanisms of tendinopathy to identify biomarkers and therapeutic targets.

b. Genomics and epigenomics

- Characterizing regulatory regions of genes relevant to musculoskeletal tissues;
- Pursuing in vivo studies such as quantitative trait loci analyses to identify genes that define properties of cartilage and joints;
- Characterizing epigenetic modifications that may relate to development of healthy tissues and chronic joint diseases;
- Exploring possible roles of epigenetic mechanisms in the differential onset and progression of musculoskeletal diseases;
- Studying mechanisms by which gene mutations and epigenetic differences contribute to musculoskeletal diseases; and
- Determining how noncoding intracellular and extracellular RNA fragments influence cell behavior in healthy and diseased or injured tissue and exploring their potential utility as biomarkers of disease.

2. Pathogenesis of osteoarthritis

Osteoarthritis (OA), the most common degenerative joint disease, affects not only articular cartilage lining bone surfaces, but also components such as subchondral bone, menisci, ligaments, capsule, synovial membrane, and periarticular muscles. Excessive, debilitating deterioration of joint tissues is a hallmark of OA – regardless of whether it is caused by an inherited mutation, a developmental or post-traumatic joint instability, a failure of the neuromuscular system to protect against repetitive loading, or metabolic events that cause excessive joint remodeling. Studies of the cellular and biomechanical factors responsible for OA onset and progression or promotion of healing and repair will likely require multidisciplinary research teams. Broad areas of potential research directions include:

a. Influence of biomechanics and injury

- Determining biomechanical factors (including gait) and biochemical pathways that influence initiation of joint changes associated with early OA, and progression of these changes to severe, late-stage OA;
- Evaluating biomechanical factors that influence joint deterioration after injury or during disease, or those that affect healing (Conduct research that may lead to potential therapeutic targets against damage to the ligaments, tendons, or menisci.);
- Mapping variations in gene expression during healing, remodeling, and adaptation to injury and disease (particularly tendinopathy), with particular emphasis on cellular and molecular signals that link mechanical loading to gene expression;
- Tracking and modeling post-injury changes in animal models to better understand the course of joint repair or deterioration and how underlying mechanisms change with sex or age; and
- Understanding basic biomechanical effects and related biochemical changes from obesity that lead to, or exacerbate, the development of OA in children and adults.

b. Inflammation

- Further elucidating mechanisms in which nutrients and inflammatory cytokines are transported among the ECM, synovial compartment, and bone marrow;
- Defining the relationship between inflammatory cytokines and biological responses in joints and identifying signaling pathways triggered by joint inflammation;

- Identifying and characterizing inflammatory factors that act on subchondral bone and synovial tissue, as well as their roles in joint degeneration;
- Distinguishing between inflammatory pathways and factors that are involved after acute injury and during chronic disease;
- Exploring contributions of obesity-associated genes to joint-damaging inflammation; and
- Studying the role of pro-inflammatory molecules, including the advanced glycation end-products associated with obesity and diabetes, in joint degradation.

Research needs and opportunities related to inflammation's role in osteoarthritis were discussed in greater detail at a 2013 NIAMS roundtable discussion.

c. Pain

- Assessing basic biological processes associated with spinal disorders and their related pain syndromes (Study the genes and molecular pathways that give rise to painful osteoarthritic joints.);
- Studying pain pathways activated during OA-induced mechanical stresses on joints (Most understanding of OA pain is based on chemical induction of disease. However, pain due to physical joint degeneration (e.g., the mechanical action of bone rubbing on bone during severe osteoarthritis) could be caused by different mechanisms.); and
- Determining why only some people with joint degeneration experience pain (Structural abnormalities are ubiquitous as people age, but pain is not.).

d. Genetic factors

- Defining the role of cellular aging and aging-associated epigenetic changes on OA onset and progression;
- Investigating mechanisms of disease in genetically defined subsets of OA;
- Comparing genetic profiles of people who develop post-traumatic OA shortly after injury with genetic profiles of those who do not (This includes identifying variations in noncoding sequences and examining differential effects on epigenetic regulation.); and
- Investigating early changes that occur in people with OA who advance to total joint replacement (One strategy would be to assemble cohorts with type II collagen defects. Advantages to studying this population include:
    - Pathogenesis and joint failure are more uniform and occur at an earlier age and
    - These individuals are motivated to participate in research.)

- Assembling large, well-characterized collections of anterior cruciate ligament injury cases and matched controls to study development of post-traumatic OA and where possible, adapting existing cohorts to genetic studies;
- Determining contributions of gene-gene and gene-environment interactions to overall genetic influence on OA susceptibility;
- Investigating the role of genetic influences on OA susceptibility, including GWAS to detect multiple genes that contribute to a given phenotype; and
- Using genetically modified mice and new tools for genetic analysis in mice and humans to understand genes involved in joint degeneration and to develop approaches for treating and preventing disease.

e. Models for studying injuries and treatments

The biological relevance of studying small animals, such as mice, for understanding adult human health is less robust than many would like. More parallels are needed between small and large animal models. Some large animals (e.g., horses, certain breeds of dogs) are predisposed to develop musculoskeletal conditions. How do large animal models compare with small animal models that also model risk for musculoskeletal disorders (e.g., guinea pigs)? How do results vary between male and female animals and among animals at different life stages, and what do these differences teach us about human physiology and treatment responses? Is it possible to agree upon a single large-animal model to parallel research that has been conducted in mice?

- Developing well-characterized, age-appropriate animal models to study OA;
- Developing and testing models that more closely resemble how people behave after injury (Many experiments are designed such that interventions are begun soon after injury, but people often wait to seek treatment.);
- Studying the local joint environment “post-injury” to identify approaches to protect tissues from damage and to promote tissue repair; and
- Examining long-term outcomes of anterior cruciate ligament repair in large animals (Current strategies for repairing torn anterior cruciate ligaments are of short-term benefit to people.).

B. Musculoskeletal Biology and Diseases: Regenerative Medicine

Regenerative medicine – tissue engineering and gene, cell, and pharmacological treatments that repair and restore tissue structure and function – is a multidisciplinary field involving both the life and physical sciences. Translational research and coordinated and collaborative research efforts play key roles in moving this field forward.

1. Multidisciplinary research teams

- Developing multidisciplinary research teams with expertise in the life and physical sciences (e.g., developmental biologists working with tissue engineers) and promoting translational research and
- Encouraging cross-disciplinary discussions on broad issues in regenerative medicine and providing opportunities for cross-training and education for emerging scientists.

2. Biological therapy development

In addition to research topics identified under Molecular and cellular biology of musculoskeletal tissues, above, broad areas of potential research directions include:

- Designing and testing methods to deliver molecular, cellular, or gene-based therapies for repair of musculoskeletal tissues including bone, cartilage, ligaments, menisci, tendons, and discs, and for OA treatment and prevention (Of particular interest are in vivo strategies to deliver cells, genes, or biomolecules.);
- Generating methods for site-specific, endogenous gene- and cell-modulation to facilitate integration of engineered tissues;
- Accelerating translation of cell-, gene-, and tissue engineering-based strategies into clinical testing by conducting studies in large animals;
- Developing and testing gene- or protein-based approaches for healing bone fractures, especially large bone defects;
- Assessing use of progenitor cells – as well as stem cells, such as iPS cells and embryonic stem cells – for musculoskeletal tissue applications (e.g., regeneration or repair of cartilage, ligaments, menisci, tendons, or discs);
- Comparing and standardizing cell sources to identify promising approaches for advancing tissue engineering and regenerative medicine beyond the laboratory and into the clinic (e.g., adult stem cells from muscle, adipose tissue, or bone marrow vs. differentiated cells such as chondrocytes; adult stem cells vs. embryonic or iPS cells);
- Developing strategies to recruit and direct endogenous progenitor or stem cells for regeneration;
- Investigating the influence of stem and progenitor cells on inflammatory and immune responses and their effects on regeneration and healing; and
- Expanding testing in preclinical models such as in large animal models for bench-to-bedside translation of regenerative medicine research (For example, development of orthopaedic implants and surgical techniques, as well as translation of the regeneration of weight-bearing musculoskeletal structures, all specifically require studying large animals.).

3. Scaffolds and biomaterials for tissue engineering

Successful tissue-engineering strategies require biomaterials and scaffolds that support structural and functional development and maintenance of regenerated or repaired musculoskeletal tissues. Studying the biology of tissue development and organization often informs the design of optimal biomaterials and scaffolds. Such materials could be used when regenerating tissues in vitro for subsequent implantation in vivo, as well as in direct in vivo tissue regeneration and repair.

In addition to research topics identified under Molecular and cellular biology of musculoskeletal tissues, broad areas of potential research directions include:

a. Material development

- Designing biomaterials and scaffolds that direct the growth, differentiation, and organization of cells, by providing appropriate physical, chemical, and mechanical cues to form functional musculoskeletal tissues that mimic natural tissues' biomechanical properties;
- Exploring innovative uses of the natural ECM as biomaterials or scaffolds to provide structural and mechanical properties appropriate for functional musculoskeletal tissues and developing biomaterials that mimic or produce functionally superior scaffolds; and
- Testing effects of biomaterials and scaffolds on the host immune system and inflammatory responses.

b. Validation

- Defining functional outcome measures to evaluate tissue-engineered products and
- Standardizing and comparing biomaterials and scaffolds to identify those with the most promise for transition from laboratory to clinic.

4. Enabling technologies

a. Methods and models

- Developing and testing minimally or non-invasive methods and devices to monitor engineered tissues, track cell fate, and deliver scaffolds in situ;
- Developing methods to control responses and interactions between cells and their local environments;
- Finding new methods to sterilize and preserve natural and synthetic materials and scaffolds to render them suitable for implantation;

- Facilitating the standardization of tissue culture reagents and protocols, safety procedures, outcome measures, testing and validation of animal models, and evaluation techniques; and
- Developing 3-D in vitro human musculoskeletal tissue model systems to study human physiology and disease pathogenesis, as well as for drug discovery and toxicity studies or for testing a proposed intervention's feasibility, function, and safety in preparation for in vivo studies (Such research on the development of tissue-engineered, cell-based models would reduce the cost of using animal models and lessen the scientific community's need to study animals.)

b. Imaging for regenerative medicine

- Developing real-time, minimally or non-invasive imaging modalities for in vivo monitoring of cell proliferation, differentiation, survival, migration, and integration;
- Developing real-time, minimally or non-invasive imaging modalities to monitor tissue-function repair and integration processes in vivo; and
- Developing non-invasive imaging methods to measure functional capacity of tissue in small- and large-animal models, and in humans.

5. Functional integration

Research on the integration of regenerated or engineered tissues within a host organism must reflect the complex physiological interactions that occur across multiple tissue types. Such systemic interactions include biological signaling processes, vascularization, innervation, and influences from the innate and adaptive immune systems. Preservation of structural and mechanical function, host and graft survival, and safety are also important.

In addition to research topics identified under Enabling technologies, above, broad areas of potential research directions include:

- Studying the impact of inflammation and immune responses on regenerative processes;
- Developing strategies to integrate engineered tissues with the host while reducing adverse effects (e.g., immunogenicity, toxicity) and considering ongoing disease progression; and
- Developing, validating and standardizing functional outcome measures that assess a treatment's effectiveness objectively.

C. Musculoskeletal Biology and Diseases: Preclinical and Translational Research into Joint Replacements

Implants such as total hip and knee replacements have been shown to be effective tools to treat end-stage arthritis that has not responded to non-operative treatment. These implants thus improve an individual's functionality and quality of life. If a joint implant fails, however, an individual may require a second surgery that is not likely to be as successful as the initial procedure. The main cause of failure is osteolysis (disappearance of bone surrounding an implant caused by a reaction to microscopic particles from an implant). Numerous research opportunities exist to develop improved biomaterials, tools to better assess implant wear, and increased knowledge of osteolysis biology and pathophysiology. Investigators are encouraged to avail themselves of data from registries of implant failures/retrievals, when appropriate.

Broad areas of potential research directions include:

1. Implant deterioration and failure

- Analyzing biologic responses (including innate and adaptive immune responses) to implant-wear particles and their role in implant failure;
- Pursuing clinical and histopathological studies to better understand, diagnose, and treat metal hypersensitivity;
- Identifying features of wear debris most critical in determining biological responses to implant-wear particles (Detailed mechanistic studies of pathogenesis of periprosthetic osteolysis and implant loosening in different joints (e.g., hip, knee, and spine) may be useful.);
- Explaining and quantifying features of third-body wear (implant debris that becomes trapped between two implant surfaces) and designing preventive strategies to counter it;
- Understanding effects of mechanical factors (e.g., motion and pressure) on implant wear and loosening;
- Elucidating effects of stress shielding on bony structures (e.g., the acetabulum) that support implants;
- Identifying biological and implant characteristics that predispose some people to develop chronic or recurrent bone infections after joint-replacement surgery; and
- Using genome-wide array analyses to understand genetic risk factors for, and their relevance to, osteolysis.

2. Improved materials and designs

- Exploring the chemistry of interactions between biologic lubricants and implant-bearing surfaces;
- Improving strength and fatigue resistance of implant materials without compromising wear and oxidation resistance;
- Developing new materials and modifying surfaces of existing materials to lessen wear and reduce failure rates;
- Developing materials that facilitate healing by stimulating implant integration and preventing infection; and
- Using data-driven design approaches to improve implant durability and performance.

3. Tools for improved implant design and testing

- Developing methods to better assess metal-on-metal implant wear, particularly in people with well-functioning implants who do not exhibit symptoms of elevated blood levels of metal ions;
- Measuring wear in total knee and hip replacements (Automated image-recognition software, for example, is one possible tool for such studies.);
- Designing models to predict functional performance or possible causes of implant failure (e.g., joint instability, excessive wear, fracture, implant loosening);
- Standardizing mechanical-testing strategies to assess performance and fracture resistance of new formulations; and
- Studying efficacy of CT and MRI scanning in implant modeling (including 3D printing) and for assessing the extent of implant osteolysis.

D. Musculoskeletal Biology and Diseases: Biochemical and Imaging Biomarkers

Many musculoskeletal diseases are chronic and have long, variable clinical courses. These conditions often take decades to develop and can be difficult to characterize. Disease progression and treatment responses are often determined through measurement of biochemical factors in blood or body fluids, or through analyses of genetic biomarkers from tissues or peripheral blood cells. Broad, innovative use of imaging techniques, in combination with measurements of biochemical markers, could also allow early identification of disease onset, predict disease progression, and enable direct monitoring of responses to tissue repair and therapeutic interventions. For many musculoskeletal conditions, responses to therapies are difficult to determine. Researchers are beginning to believe that, as with many disorders, a battery of several biomarkers may be more useful than a single one.

The box, "Osteoarthritis Initiative (OAI)" describes an NIH effort to create a public resource to validate imaging and biochemical biomarkers for OA.

In addition to opportunities regarding biomarkers and imaging methods described under Preclinical and Translational Research into Joint Replacements, above, broad areas of potential research directions include:

1. Identification, qualification, and validation

- Broadening biomarker research to address genetic markers of disease or markers that may predispose individuals to a heightened risk of disease progression, worsening, and severity, or research that predicts treatment response via biomarkers;
- Conducting basic exploratory studies to identify lead candidate biomarkers;
- Developing and applying new technologies to discover biomarkers of disease onset, progression, and treatment response;.
- Identifying post-injury joint changes that cause or predict OA;
- Identifying biomarkers useful for predicting overall outcomes or those in specific subsets of people (Of particular interest is the use of existing repositories and databases to qualify and validate biochemical and structural changes associated with OA onset and progression.);
- Combining markers of cartilage and bone catabolic activity, imaging markers, proinflammatory cytokines, and gait-analysis data to determine optimal timing of joint replacement in OA, and to identify people at risk of implant failure; and
- Studying non-invasive biomarkers to facilitate early diagnosis and to monitor treatment of musculoskeletal infections, including those surrounding implanted devices.

Osteoarthritis Initiative (OAI): A limited number of therapies exist for osteoarthritis (OA) treatment. Most only relieve pain and reduce disability; no current therapy slows or halts disease progression. One barrier to the development of drugs that block underlying causes of OA symptoms is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To overcome this problem, NIH – with input from FDA – partnered with private sponsors to create the OAI. When completed, the effort will provide an unparalleled state-of-the-art database showing both the natural progression of OA as well as information on risk factors, joint changes, and outcome measures. All data are freely available to researchers worldwide. Researchers will be able to pose hypotheses about possible OA biomarkers of disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease development and severity. Scientists can also use the OAI to identify potential disease targets and to develop tools for measuring clinically meaningful improvements.

By the end of FY 2014, investigators will have collected survey, clinical, and image data and biological samples from approximately 4,800 people at baseline, 12-, 24-, 36-, 48-, 60-, 72-, 84-, and 96-month time points.

For further information, see the OAI page on the NIAMS website.

2. Resource development and application

- Applying existing and newly developed imaging technologies when studying disease and identifying possible imaging biomarkers associated with disease onset and progression;
- Creating and standardizing multiplex arrays that simultaneously measure multiple biomarker candidates in a single sample;
- Developing imaging technologies and systems biology approaches and applying them to the discovery of biomarkers of OA disease onset, progression, and treatment response;
- Producing and assembling resources to assist investigators conducting biomarker development and validation studies;
- Standardizing imaging methods across study sites to facilitate data sharing and comparison;
- Developing image-registration methods for use in longitudinal studies;
- Standardizing methods to evaluate changes in human joint structure – synovium, cartilage, bone, ligaments, tendons, and menisci – associated with normal aging (Differentiate these changes from those associated with symptomatic joint diseases like OA.); and
- Employing existing infrastructure, such as databases and clinical cohorts, to

transition promising biomarkers from laboratory to clinic through application of state-of-the-art statistical, analytical, and computational methods.

E. Musculoskeletal Biology and Diseases: Clinical Research

Characterization of disease in the context of clinical studies may enable researchers and health care providers to distinguish between disease subtypes that produce similar endpoints (e.g., OA, connective tissue injuries). The NIAMS research portfolio includes a number of large clinical trials and cohort studies (e.g., the OAI, see box "Osteoarthritis Initiative (OAI)") that researchers could mine for information about variations in risk factors, disease manifestation, and clinical outcomes.

As investigators consider clinical studies of musculoskeletal and orthopaedic conditions and trials of potential diagnostic strategies and treatments related to the broad areas described below, they are encouraged to consider the following issues:

- The role of personalized medicine in maintaining or restoring musculoskeletal health;
- Assessment of effectiveness, as well as efficacy, for reducing pain and improving function;
- The importance of measuring a combination of outcomes so that results are meaningful to individuals and health care providers;
- The use of registries, electronic medical records, and large databases to perform clinical studies;
- The feasibility of using a central institutional review boards for multi-site clinical projects; and
- Integration of social media and technology into clinical studies to make research more efficient (i.e., more powerful and less expensive).

1. Behavioral and psychosocial research

Behavioral and psychosocial factors are involved in the onset, course, and outcome 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 effectiveness of prevention and treatment. Interdisciplinary research that integrates behavioral and biomedical sciences is likely to result in enhanced management of, and reduced disability from, chronic diseases and, and may shed light on complex mechanisms involved in pathogenesis.

Research needs and opportunities were discussed in 2010 at a roundtable on Psychosocial and Behavioral Therapies for Musculoskeletal and Rheumatic Disease Outcomes. Broad areas of potential research directions include:

- Assessing the willingness of individuals belonging to racial and ethnic sub-populations in the United States to undergo total joint replacement and developing strategies to ensure that all Americans who have severe OA can make the best possible decisions regarding their treatment;
- Determining mechanisms and outcomes of behavioral therapies for treating chronic musculoskeletal conditions and injuries;
- Developing and validating accurate and appropriate outcome measures for studying disability related to musculoskeletal conditions and injuries;
- Clarifying the impact that psychological distress has on recovery after musculoskeletal trauma and designing strategies to prevent or reduce it;
- Determining which outcomes of musculoskeletal diseases and procedures are influenced by modifiable attributes such as beliefs, attitudes, and psychological states and pursuing strategies to improve health;
- Determining which behavioral interventions can be delivered by someone other than a physician without losing effectiveness; and
- Exploring strategies to sustain behavioral interventions known to be effective (e.g., weight loss).

2. Childhood musculoskeletal conditions

The cost of childhood musculoskeletal conditions is enormous. Although some conditions can be treated effectively, resulting in full restoration of an active life, others can result in early death or progressive problems into adulthood. Still others present lifelong challenges for the affected individual, his or her family, and society.

Prevention of childhood injury is addressed under Fractures and other types of musculoskeletal trauma, below. Other broad areas of potential research directions include:

- Developing physiological interventions to correct skeletal deformities and neuromuscular disorders, including muscular dystrophies and
- Studying musculoskeletal implications and complications of rheumatic diseases in children (Examples include growth delay, osteoporosis, and avascular necrosis.).

3. Osteoarthritis

OA is by far the most common type of arthritis, and age is a prominent risk factor. Although OA affects an estimated 27 million Americans age 25 and older, very few, if any, disease-modifying agents exist. Healthy People 2020 includes several objectives related to improved overall health and functioning of people who have arthritis.

Broad areas of potential research directions include:

a. Risk factors

- Defining and stratifying OA risk factors in individuals and in populations (Risk factors include body weight, previous joint injury, family history, diet, physical activity, coincident pathology of other tissues and organs, and medication use.);
- Determining effects of changes in modifiable risk factors on OA onset and progression; and
- Developing or modifying strategies, including preventive and rehabilitative approaches, to reduce the development of disability and functional limitation associated with OA onset and progression.

b. Treatments (also see Joint replacement, below, and Behavioral and psychosocial research, above)

- Exploring rehabilitation and physical-therapy strategies to reduce risk for impairment from OA progression;
- Identifying and characterizing agents and methods to decrease disability and pain from OA-related tissue degeneration;
- Investigating strategies to prevent or reverse structural modifications of diseased joints and identifying new targets/developing corresponding therapeutic agents; and
- Pursuing innovative treatments (such as biologics) to slow or prevent joint degeneration.

4. Joint replacement

As described in Preclinical and Translational Research into Joint Replacements, above, implants for total hip and knee replacements are effective treatments for people with end-stage arthritis. Although infection at the site of a total joint replacement is rare, it can be devastating and require lengthy hospitalization. Other complications include implant loosening or failure, both of which require additional surgeries that are less likely to be as successful as the initial joint replacement. In addition to preclinical research examples noted in Preclinical and Translational Research into Joint Replacements and Biochemical and Imaging Markers, above, broad areas of potential patient-oriented research directions include:

a. Outcomes

- Analyzing outcomes of revision total knee and hip replacements (Such studies could be useful for identifying grafting techniques that lead to well-fixed implants,

defining the roles of bone and synthetic graft materials, and quantifying graft incorporation and bone resorption.);

- Developing and implementing strategies to prevent implant-related musculoskeletal infections, their transition to chronic infections, and their post-treatment recurrence;
- Investigating effects of anabolic agents administered post-operatively to see whether they can significantly increase implant osteointegration and decrease subsequent loosening;
- Testing long-term biocompatibility and wear properties of alternative-bearing surfaces; and
- Standardizing criteria for determining therapeutic effects of non-surgical interventions (such as drugs or rehabilitation strategies) to prevent or treat implant osteolysis (This will enable comparison of interventions across different studies.).

b. Techniques and timing

- Assessing impact of small-incision, minimally invasive surgical approaches and robotic surgery on functional outcomes, complications, and revision rates;
- Developing and validating pre- and post-operative rehabilitation strategies, especially for hip and knee replacement;
- Improving links between implant-improved performance and surgical/patient characteristics; and
- Studying the clinical and economic impact of earlier diagnosis of implant osteolysis.

5. Spinal disorders

Many spinal disorders are common, costly, and potentially disabling. Low back pain affects millions of people globally and exerts an enormous socioeconomic impact. A frequent cause of disability, low back pain causes employees to lose many days of work each year. Its costs to society – and opportunities to reduce those costs – earned its position as a Healthy People 2020 objective, "Reduce activity limitation due to chronic back conditions." Although low back pain is an important public health issue, little is known about its causes. A considerable investment in a study of surgical and non-surgical therapies for common causes of low back pain has yielded important results (see box, "The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain"). However, much remains to be discovered about strategies to improve the lives of people affected by back pain or related conditions. To facilitate research on chronic low back pain, an NIH task force developed research standards that include defining chronic low back pain, assessing its impact on people's lives, identifying the minimum dataset

that should be collected in chronic low back pain research, and defining optimal outcomes to evaluate treatment effectiveness.

Broad areas of potential research directions include:

- Developing and evaluating new treatment methods and technologies for degenerative disc disease, including use of an artificial disc and nucleus and use of regenerative medicine techniques to reverse disc degeneration;
- Pursuing clinical studies to address management of spinal disorders for which consensus regarding preferred treatment is lacking;
- Studying efficacy and effectiveness of current and emerging technologies for treating spinal disorders; and
- Facilitating mechanistic and outcomes research across disciplines through the continued development and use of common data elements and terminology.

The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain: World-wide, low back pain is the leading cause of disability, as measured by years lived with disability (YLDs), and it is the sixth greatest source of disease burden as measured in disability-adjusted life years (DALYs).[1] The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain is collecting data to help individuals and their health care providers determine the most appropriate treatment for this common, disabling condition.

Before SPORT, many people with chronic low back pain were conflicted about whether to undergo surgery: Some were not sure surgery was worth the risk, while others feared that delaying surgery might cause even more damage. SPORT has demonstrated that, indeed, surgery is better than nonoperative treatments for the three most common causes of severe low back pain: intervertebral disc herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (vertebrae slipping). Importantly, though, SPORT results show that people who have one of these conditions are not subjecting themselves to further harm if they adopt a “wait-and-see” approach before committing to surgery.

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SPORT, continued.

This research showed that benefits from surgery to correct spinal stenosis, for example, appeared as early as six weeks after surgery.[2,3] Those individuals with severe slippage and discomfort due to lumbar spinal stenosis with degenerative spondylolisthesis seemed to benefit the most.[4] Although people who did not have surgery reported some improvement two years into the study, those who had surgery seemed to be doing considerably better than those who did not.[2,3] Additionally, SPORT showed that combining two surgical procedures – decompressive laminectomy and fusion – did not benefit individuals with lumbar spinal stenosis without degenerative spondylolisthesis any more than did decompressive laminectomy alone.[5] The findings for individuals with intervertebral disc herniation were equally meaningful. Two and four years after surgery, SPORT results showed that individuals who had surgery for a herniated upper lumbar disc felt significantly better than those who had had a lower disc repaired.[6,7] Although lumbar discectomy is more costly than medications and/or physical therapy, this research shows it is a cost-effective treatment.[7]

Benefits from surgical intervention occurred for all conditions at four years,[8,9,10] and for disc herniation at eight years.[11] Eight-year results for the other two conditions are pending. Of note, those individuals with disc herniation who continued to participate in SPORT eight years after joining the study reported consistent results between their four- and eight-year surveys, regardless of whether they had surgery or not.[11]

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6. Fractures and other types of musculoskeletal trauma

In addition to treatment-associated health-care expenditures from fractures and other types of musculoskeletal trauma, these conditions cost billions of dollars in terms of lost employment. Traumatic musculoskeletal injuries can lead to lifelong disability. Trauma

is the leading cause of death after the first year of life, exceeding all other causes of childhood death combined. Treatment of people with fractures in conjunction with trauma to other organ systems (e.g., traumatic brain injury) is a challenge 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 after fractures or skeletal trauma will improve patient outcomes, enhance the lives of patients and their caregivers, and facilitate their return to the workforce.

In addition to the relevant Behavioral and psychosocial research opportunities, above, broad areas of potential research directions include:

a. Prevention

- Elucidating mechanical forces that contribute to or cause joint injuries (e.g., ACL tears, herniated discs) and understanding consequences of cumulative trauma disorders of soft tissues (Such studies could be useful for preventing injuries and developing protective devices for preventing these injuries.);
- Explaining the role personalized medicine can play in maintaining bone and joint health;
- Preventing childhood/adolescent injuries; and
- Assessing effectiveness of strategies for preventing soft-tissue injuries in children and adults.

b. Management

- Further establishing outcomes and cost-effectiveness of treatments for specific fractures and other musculoskeletal injuries, including those of ligaments, tendons, and other musculoskeletal soft tissues.

i. Fractures

- Developing and validating measures that better assess fracture healing;
- Testing methods to diagnose and treat injuries to and around growth plates, to prevent growth disturbances;
- Improving strategies for repairing fractures in older people;
- Refining prevention, diagnostic, and treatment strategies related to chronic or recurrent bone infection following limb trauma; and
- Enhancing fracture healing through bone grafts and other implant materials, including the use of growth factors.

ii. Damage to cartilage, connective tissue, and fibrocartilaginous tissues (including menisci)

- Improving diagnostic methods and treatments of focal cartilage defects, subchondral bone changes, and other types of joint damage to prevent post-traumatic OA;
- Optimizing methods of repairing or replacing damaged ligaments and menisci to reduce pain and dysfunction and to improve long-term outcomes;
- Improving strategies to diagnose and treat symptomatic rotator-cuff tears; and
- Exploring the natural history of rotator-cuff tears to understand why some are more symptomatic than others.

iii. Trauma to multiple organ systems

- Enhancing strategies to recognize and treat combined injuries, especially as they relate to the timing and type of surgery in people subjected to multiple traumatic insults (e.g., those suffering fractures in addition to head injury, chest and/or abdominal injury, or shock). (As with other research or clinical practice that involves multiple tissues and organ systems, work in this area will likely involve teams of investigators with expertise in multiple disciplines.); and
- Improving surgical strategies to correct injuries affecting multiple systems such as compartment syndromes and mangled extremities.

c. Study design

- Implementing strategies to standardize clinical studies of interventions that influence fracture and soft-tissue healing, using both objective and subjective parameters.

7. Sports and fitness

Fitness is associated with good health and a sense of well-being. Numerous studies have shown beneficial effects of exercise in disease prevention, yet one problematic feature of exercise is potential injury. Musculoskeletal soft tissues are vulnerable to injury and damage as the result of overuse and/or trauma. These injuries are often life-altering. In addition, cartilage loss that leads to joint degeneration is generally slow and progressive with age, and thus it may be difficult to monitor over time.

In addition to examples noted under Osteoarthritis and Fractures and other types of musculoskeletal trauma, above, broad areas of potential research directions include:

a. Physical activity requirements

- Acquiring better understanding of how particular fitness requirements vary with sex, age, and conditions that limit mobility (Such knowledge is important for efforts to encourage physical fitness and promote health.) and
- Identifying markers of bone, cartilage, and muscle quality that could facilitate studies into which types of exercise are optimal for promoting musculoskeletal health.

b. Injury prevention

- Characterizing sex differences in ultra-high performance sports as the groundwork for development of focused programs to prevent injuries and overuse disorders commonly seen in these athletes.

c. Treatment and rehabilitation

- Applying physical medicine and rehabilitative strategies to soft-tissue injuries, to restore maximal function and
- Determining types and levels of exercise effective for minimizing progression of specific diseases and promoting restoration of musculoskeletal function (Such knowledge could translate into "exercise prescriptions.").

V. MUSCLE BIOLOGY AND DISEASES

NIAMS muscle biology and diseases programs encourage basic, translational, and clinical research on the biology and disorders of skeletal muscle. Studies address questions about muscle developmental biology, growth, maintenance, and hypertrophy; physiology of muscle contraction; structural biology of the contractile apparatus; mechanisms of muscle diseases and disorders; biomarkers and outcome measures for clinical and preclinical studies; and natural histories of muscle conditions. These programs also support development and testing of therapies for muscle diseases and disorders, including cell and gene therapies, small molecule drugs and biological products, and exercise and other physical interventions. In addition to research projects, NIAMS supports research training and career development and scientific conferences and research infrastructure – such as core facilities that enhance and accelerate NIH-funded research and that sponsored by other public and private organizations.

Muscular dystrophies are an area of emphasis within the NIAMS muscle research portfolio. NIAMS participates in the Muscular Dystrophy Coordinating Committee (MDCC), which includes stakeholders from Federal and private organizations. Research objectives for muscular dystrophies will be presented in this NIAMS Long-Range Plan

where they overlap with objectives for other muscle diseases. A more specific and detailed description of research objectives for muscular dystrophies is found in the MDCC's Action Plan for the Muscular Dystrophies (see box, "Action Plan for the Muscular Dystrophies"). The plan – which the MDCC is updating, with input from experts in the fields of muscular dystrophy pathophysiology, diagnosis, treatment, and patient and family care – will be available in FY 2015 at https://mdcc.nih.gov/.

Action Plan for the Muscular Dystrophies: As the lead agency of the Muscular Dystrophy Coordinating Committee (MDCC), NIH is coordinating the revision of the MDCC Action Plan for the Muscular Dystrophies. As with the 2005 plan, the 2015 document (which will be available at https://mdcc.nih.gov/ will reflect scientific opportunities in:

- Disease mechanisms;
- Diagnosis and screening;
- Preclinical therapy development;
- Clinical development; and
- Living with muscular dystrophy.

Priorities will reflect the expertise and judgment of leading basic and clinical researchers, physicians, and patient advocates who are devoted to the field of muscular dystrophy. As the Action Plan is being developed, NIAMS is identifying areas of synergy between the Institute's Long-Range Plan and the MDCC Action Plan, with the goal of coordinating efforts to advance knowledge about the basic mechanisms underlying diseases and to support translational and clinical research focused on finding treatments.

A. Muscle Biology and Diseases: Skeletal Muscle Biology

1. Cell and Developmental Biology

Understanding healthy and diseased muscle states requires basic research on skeletal muscle tissue development and maintenance. Studies of pathways controlling muscle formation, for example, are likely to have implications both for diseases characterized by muscle deterioration, and for regeneration of muscle after injury. Understanding natural repair processes after injury or while recovering from disease could lay the foundation for improved therapies. Read more details about opportunities that could be facilitated by basic studies of muscle's anabolic processes.

Broad areas of potential research directions include:

a. Development

- Defining factors that influence embryonic cell fate and those that control cell proliferation, migration, and differentiation in myogenesis;
- Elucidating mechanisms underlying myogenic chemotaxis, adhesion, and fusion;
- Determining when individual myonuclei are incorporated into muscle tissue during development and their progenitor cell sources;
- Identifying and characterizing determinants of tissue patterning (e.g., muscle size, shape, fiber composition) during development;
- Studying formation of the contractile apparatus, myotendinous junctions, and other complex structures that make up mature muscle; and
- Understanding how muscle fibers integrate with other tissues (e.g., adipose tissue, immune cells, and tendons) during development.

b. Growth and maintenance

- Characterizing cell types that contribute to muscle growth and maintenance (Studies on the activation, migration, proliferation, and differentiation of muscle stem cells, including satellite cells and other progenitors, during cell or tissue turnover and repair are of interest.);
- Exploring satellite cell heterogeneity (Individual fibers or muscles may have specific subpopulations of satellite cells, and there may be differences between species.);
- Determining when individual myonuclei become incorporated into muscle tissue during hypertrophy and their progenitor cell sources;
- Examining functional and gene expression differences among muscle fibers or myonuclei and uncovering those differences (e.g., in gene expression patterns) responsible for muscle specialization;
- Defining factors that regulate gene and protein expression controlling muscle growth, fiber type determination, and hypertrophy (e.g., epigenetic changes, microRNAs);
- Identifying and characterizing modulators of signaling pathways that increase muscle-fiber growth and cell proliferation (e.g., myostatin inhibitors, IGF1 signaling agonists);
- Defining genetic variations that enhance or limit normal anabolic responses of skeletal muscle to resistance or endurance training or that protect from or exacerbate atrophy or cachexia;

- Investigating tissue, cellular, and subcellular responses to environmental factors including exercise, disuse, or nutrition;
- Exploring molecular and biochemical changes responsible for differences in muscle mass, susceptibility to atrophy, and response to exercise that are seen in men and women, in people at different ages, or in people from different racial backgrounds; and
- Studying the catabolic processes of autophagy and proteolysis as they relate to turnover of muscle fiber components.

2. Cell Physiology and Biophysics

Studies of normal muscle-cell physiology are likely to uncover new pathways and processes that researchers could use to develop treatments for muscle diseases.

Broad areas of potential research directions include:

a. Excitation/contraction coupling

- Determining structures and functions of components of the sarcolemma and sarcoplasmic reticulum required for muscle cell excitation and intracellular calcium handling (Studies of how membranes communicate are also of interest.) and
- Defining calcium's role in contraction and exploring strategies to restore muscle function by optimizing intracellular, compartmental, and extracellular calcium concentrations and sequestration (Ions other than calcium are also of interest.)

b. Structural biology and biophysics

- Elucidating structure and function of macromolecular complexes essential for skeletal muscle function and maintenance, including dystrophin/glycoprotein complex, contractile apparatus, and ion channel complexes and
- Better characterizing protein complex assembly, including roles of chaperones.

c. Cellular biomechanics

- Determining mechanisms by which mechanical stimuli influence muscle assembly and turnover;
- Determining relationships of muscle protein synthesis and force production during hypertrophy and atrophy;
- Better characterizing how the contractile apparatus and links to the ECM are modulated during fiber repair and regeneration; and

- Investigating how muscle-strain injuries affect the components and organization of macromolecular complexes.

d. Mitochondrial biogenesis, turnover, and function

- Understanding better control of muscle mitochondrial function and turnover in normal and disease states;
- Understanding effects of exercise on mitochondrial biogenesis; and
- Understanding better muscle mitochondrial function and uncoupling in energy metabolism.

3. Integrated Physiology and Metabolism

Studying muscle as a system that interacts with other tissues and organs will provide insights into the weakness and fatigue that occur with numerous non-muscle diseases. This research will also explain how physical activity contributes to overall health and well-being beyond simply improving muscle strength and cardiovascular fitness. These emerging areas of research have garnered considerable attention in recent years and were the topics of two NIAMS-sponsored roundtables (see boxes, "Mechanisms of Exercise-Induced Health" and "Impact of Muscle Physiology Research on Common Diseases and Disorders"). Both meetings emphasized that characterizing mechanisms responsible for connections between muscle and other organ systems will likely entail collaborations among researchers from multiple disciplines.

Broad areas of potential research directions include:

a. Muscle as an endocrine organ and metabolic tissue

- Defining metabolic and hormonal interactions among muscle, bone, and fat during normal, exercise, and disease states;
- Examining muscle's role as a heat-producing organ in the regulation of core temperature;
- Exploring temperature effects on muscle function;
- Identifying and characterizing factors released into circulation during skeletal muscle activity that affect other tissue and organ systems;
- Investigating compounds that improve muscle's ability to metabolize energy sources; and
- Understanding control of muscle protein synthesis and degradation, since muscle serves as an amino-acid source for other tissues in healthy and disease states.

Mechanisms of Exercise-Induced Health: Moderate to vigorous activity benefits the human body in many ways. Although exercise is associated with lower rates of

obesity, even obese individuals can enjoy the positive effects of physical activity independent of its effect on weight. Biological changes associated with better health include a less atherogenic lipid profile, greater insulin sensitivity, lower arterial stiffness and blood pressure, better endothelial function, higher bone density, muscular strength and endurance, and aerobic fitness. Improved mental health (e.g., less anxiety, less depression, a more positive self-concept) is an additional, well-documented result of physical exercise.

Provocative scientific research that addresses the cellular changes that contribute to exercise-induced improvements is beginning to emerge.[1,2] Additional work leading to a more complete understanding of the mechanisms linking regular exercise to disease prevention and improved health could contribute to decreased burden of common diseases and a significant increase in quality-adjusted life years for many people. Better understanding of the processes connecting exercise and disease prevention/amelioration may also contribute to the efficacy of physical activity as a treatment for multiple health conditions.

Get more information about research needs and opportunities regarding the molecular and cellular mechanisms by which exercise contributes to health.

[1] Owusu-Ansah E, et al. Cell. 2013. PMID: 24243023
[2] Lira VA, et al. FASEB J. 2013. PMID: 23825228

Impact of Muscle Physiology Research on Common Diseases and Disorders: Diseases and conditions such as musculoskeletal atrophy due to disuse, age-associated sarcopenia, cachexia (as seen with chronic heart failure, sepsis, severe burns, cancer, HIV/AIDS, and other disorders), debilitating muscle fatigue, and heat illness all involve perturbations to normal skeletal muscle physiology. While support of clinical trials and population studies in these areas commonly falls under other NIH components' missions, NIAMS remains interested in understanding mechanisms by which these conditions affect muscle physiology.

Read more information about how muscle research could inform prevention and treatment of common diseases and disorders, and examples of how studies of these diseases could inform understanding of muscle physiology.

b. Immune and inflammatory responses

- Characterizing positive and negative effects of inflammation on regeneration after exercise, injury, or disease (Better understand interactions of muscle cells with lymphocytes and macrophages.) and
- Determining mechanisms by which exercise alters immune responses and determining the role of inflammation on impairing or restoring function in muscle and other tissues.

c. Kinesiology

- Understanding better interactions of muscle and muscle connective tissue and the potential role played by associated structural molecules.
- Improving understanding of how mechanical function of individual muscles determines energy use; and
- Determining how muscle differentially recruits fast and slow motor units.

4. Pathophysiology

Just as research on normal muscle physiology is likely to uncover new molecular treatment targets, a better understanding of how specific molecular defects produce the abnormal phenotypes of muscle diseases will provide insights into normal muscle function.

Broad areas of potential research directions include:

a. Mechanisms of single gene muscle diseases

- Identifying gene mutations associated with muscle diseases with unknown causes ;
- Further characterizing genotype-to-phenotype correlations for muscle diseases;
- Better understanding mechanisms of diseases caused by single-gene mutations, such as muscular dystrophies and channelopathies (Through hypothesis-driven studies, characterize disease mechanisms to uncover potential therapeutic targets and to better understand normal muscle biology.);
- Elucidating how defects in post-transcriptional processing – including splicing, transcript modification, localization, and transcript stabilization or degradation – contribute to muscle diseases;
- Further understanding mechanisms of muscle disease involving defects in post-translational processing such as glycosylation;
- Examining factors responsible for selective targeting of muscle groups or individual muscles by disease processes while sparing other muscles;
- Identifying compensatory gene products (e.g., utrophin for mutated dystrophin) and developing strategies to control their expression, accumulation, localization, and activity; and
- Characterizing effects of modifier gene variations and epigenetic modifications on muscle disease onset, severity, and progression.

b. Muscle impairment associated with complex diseases and conditions

- Exploring mechanisms that cause muscles and bones to atrophy during prolonged bed rest (often in the context of a critical illness such as cancer);
- Investigating skeletal muscle changes in cachexia (as it occurs with diverse conditions including AIDS, cancer, chronic obstructive pulmonary disease, congestive heart failure, and end-stage renal failure);
- Determining causes and effects of age-associated sarcopenia at subcellular, cellular, and tissue levels;
- Identifying and characterizing shared signaling pathways associated with downstream pathologies (such as weakness and muscle wasting) common to many genetic and acquired diseases;
- Studying disorders arising from environmental factors, including statin-induced myopathies and researching the genetic and environmental factors contributing to these conditions;

- Determining how muscle fatigue or pain is associated with chronic or acute diseases of other organ systems (Elucidate mechanisms responsible for muscle pain.);
- Characterizing genetic and gene-environment interactions associated with complex muscle diseases such as inflammatory myopathies; and
- Studying the role of muscle in inflammatory myopathies to facilitate development of interventions that target muscle and not just the immune system.

c. Fibrosis and scarring

- Elucidating cellular and molecular events that contribute to, or prevent formation of, fibrosis and scarring during disease progression and in response to injury;
- Determining whether muscle fibrosis is a reversible event and understanding steps involved in this process; and
- Characterizing genetic modifiers of muscle fibrosis and scarring and testing gene products as potential therapeutic targets or prognostic biomarkers.

B. Muscle Biology and Diseases: Preclinical Translation and Therapy Development

1. Development and use of model systems

Cellular and animal models enable research into disease mechanisms and therapeutic target identification. Models also serve as testing grounds for candidate therapeutics.

The NIAMS and other Institutes support infrastructure (e.g., through the Wellstone Muscular Dystrophy Cooperative Research Centers program) to facilitate studies that involve cellular and animal models.

Broad areas of potential research directions include:

a. Animal models for understanding disease mechanisms and testing therapeutics

- Developing and characterizing additional mouse models that more accurately reflect the genetics, pathophysiology or clinical phenotypes observed in people with muscle diseases;
- Establishing additional mid-size and large animal models systems to facilitate preclinical testing of candidate therapeutics in systems closer to the dimensions, biomechanical forces and immune responses of humans;
- Developing additional animal models of muscle injury and regeneration, weakness, fatigue, pain, and other common conditions affecting skeletal muscle;
- Improving the research community's access to animal models;

- Making full use of published standard operating procedures and existing facilities for testing interventions in animal models of muscle diseases (Continue to document and publicize additional standard operating procedures where needed.); and
- Further exploring use of xenograft models that involve tissue derived from cells from people with muscle disease residing in a host animal.

b. Human induced pluripotent stem (iPS) cells and other cells as disease model systems

- Creating human cell models to study disease mechanisms and pathophysiology;
- Developing additional cell-based high-throughput assays suitable for screening libraries of small molecules and other bioactive compounds;
- Establishing human cell-based models for assessing candidate therapeutics;
- Facilitating personalized medicine strategies by making cell models from individuals for the identification of compounds to which those individuals respond; and
- Studying iPS cells from multiple individuals to identify factors responsible for variations in treatments response.

2. Preclinical therapy development

Several candidate therapies for muscle diseases, especially muscular dystrophies, have emerged in recent years. These include small molecules that act on cell or molecular processes, biologics such as antibodies or enzymes, gene and cell approaches, nucleic acids (e.g., oligonucleotides), as well as physical interventions such as vibration. Therapies are being developed by investigators in academic institutions and by small and large companies. In addition to the development of novel interventions, drugs that have already been developed for non-muscle diseases are now being tested for their potential use on muscle diseases (a process called drug repurposing). Some interventions that are being developed for rare muscle diseases, such as myostatin inhibitors, have potential for applications in other muscle diseases and in more common conditions.

Broad areas of potential research directions include:

a. Repurposing and modifications of existing drugs

- Exploring mechanisms of drugs currently used to treat muscle disease (For example, deciphering genetic and molecular mechanisms by which corticosteroids benefit people with muscle diseases may enable the development of drugs that are more efficacious or cause fewer unwanted side effects.);

- Performing high-throughput screens of molecular libraries to identify compounds that can augment existing therapies for muscle diseases and disorders;
- Pursuing pre-clinical studies in muscle-disease models for drugs approved for other diseases; and
- Studying how exercise regimens and/or nutritional supplementation can affect progression of muscle diseases and disorders or response to other therapies.

b. Developing novel interventions

i. Small molecule drugs

- Developing robust assays for use in high-throughput screens that take full advantage of the knowledge of mechanisms of muscle diseases to target important steps in pathophysiology (Consider assays and screening strategies that go beyond the traditional chemical space.);
- Utilizing available facilities and resources for high-throughput screening, chemical synthesis and modification, and pharmacology and toxicology testing (Examples include the NIH Molecular Libraries and Imaging Program and NCATS Bridging Interventional Development Gaps Program);
- Creating screening approaches specialized for muscle biology; and
- Establishing partnerships with companies and voluntary health organizations that increase the likelihood of successfully developing candidate therapeutics for testing in clinical trials.

ii. Biologics

- Exploring development of biologics for treating muscle diseases, based on activities of growth factors, extracellular matrix proteins, enzymes and other gene products;
- Characterizing isoforms, subcomponents, metabolites and mechanisms of action of potentially therapeutic proteins and other biologics;
- Broadening use of enzyme-replacement therapies beyond glycogen-storage diseases and developing strategies to prevent or manage immune response to enzyme-replacement therapy;
- Developing therapeutics that enhance muscle strength and resistance to fatigue; and
- Identifying and testing therapeutics that enhance or replace effects of exercise training on skeletal muscle.

iii. Gene therapies

- Further characterizing properties of gene-therapy vectors and serotypes to select those that facilitate efficient delivery of therapeutic genes and that minimize immune responses;
- Continuing to develop approaches to controlling gene activity (e.g., regulatory cassettes) that maximize expression of therapeutic genes in specific target tissues;
- Testing routes and strategies for delivering gene therapies to muscle groups;
- Developing a more thorough understanding of immune responses to gene therapies (Use this knowledge to avoid or minimize immune responses following initial and repeated delivery of therapeutic genes.); and
- Advancing strategies for preparation of gene therapeutics that increase scale of production, reduce costs, and optimize purity and activity.

iv. Cell therapies

- Characterizing abilities of growth factors, extracellular matrix molecules, scaffolds, or transcription factors to stimulate the engraftment, survival, proliferation, and differentiation of cells that participate in muscle regeneration;
- Comparing migratory and regenerative potential of different cell types to establish criteria associated with expansion, migration, differentiation, and stability of muscle cells and with long-term maintenance and function of muscle tissue for clinical studies;
- Producing markers for tracking long-term outcomes of cell-based muscle therapies in animal models or in people with muscle disorders;
- Studying immune responses in muscle to transplanted cell types and factors in the environment of diseased or injured muscle that affect engraftment; and
- Exploring strategies for genetic manipulation of potentially therapeutic cells by viral vectors, genome-editing technologies (e.g., CRISPR/Cas, TALENs), or other approaches to correct mutations or otherwise enhance regenerative capacity.

v. Molecular therapies (including oligonucleotides)

- Continuing to develop oligonucleotides and other strategies to edit or down-regulate the expression of gene products with the goal of compensating for mutations and restoring functions of proteins necessary for healthy muscle;
- Further developing chemistries to synthesize molecular therapies and modifications to molecules that improve their efficiency to access skeletal muscle, heart, and other affected tissues; and

- Further characterizing gene products resulting from exon-skipping strategies and evaluating the ability of those products to restore normal muscle function.

c. Behavioral and mechanical therapies

Behavioral and mechanical therapies have the potential to improve outcomes in muscle diseases when used either instead of, or in conjunction with, pharmacological treatments. Exercise interventions and biomechanical treatments are included in this category. Some of these interventions, such as prescribed physical-activity programs, could be tested in clinical studies without the need for prior animal studies, since the effects on human subjects may be quite different from those in animals. Alternate approaches such as vibration or other types of periodic forces would most likely benefit from animal studies to justify their safety, mechanisms of action, and potential for efficacy in subsequent clinical trials in humans.

Broad areas of potential research directions include:

- Leveraging knowledge about effects of mechanical stimuli on healthy and diseased muscle to develop biomechanical interventions such as vibration or period loading and
- Studying mechanisms of exercise with the goal of developing physical activity-based interventions attractive to, and convenient for, people.

C. Muscle Biology and Diseases: Clinical Translation

Clinical translation for muscle diseases includes observational studies and clinical trials. Observational cohort studies serve several purposes including collecting data that may inform hypotheses regarding mechanisms of disease, developing biomarkers and outcome measures, acquiring data needed for the design of clinical trials, and characterizing patients that would be candidates for participation in future trials. Clinical trials are needed to test the numerous interventions described above.

1. Observational cohort studies of muscle diseases

- Continuing to characterize pharmacodynamic biomarkers from blood and urine of people with muscle disease (These may include proteins, metabolites and nucleic acids (e.g., microRNAs).);
- Developing sensitive, accurate, and robust assays to measure proteins and other gene products found in muscle biopsies (These assays would be used to assess the restoration of these products in clinical trials.);

- Establishing imaging biomarkers (e.g., as measured by MRI or ultrasound) that are non-invasive and provide information about the size, shape, structure, composition, physical properties, and metabolic function of whole muscles or muscle groups (Further development of imaging methods can be facilitated by additional interactions among muscle-disease researchers, imaging physicists, and bioinformatics experts. The muscle research community should continue to adopt imaging advances from other fields such as neurology.);
- Continuing to refine approaches for measuring muscle contraction, force production, musculoskeletal function, motor control, and other physiological functions;
- Integrating approaches such as elastography or electrical impedance myography into development of biomarkers that reflect physical properties of skeletal muscle;
- Developing surrogate markers that can be quantified non-invasively and can predict changes in physical function, disease severity, development of complications, or treatment response;
- Defining outcome measures and markers that reflect meaningful changes in how an individual feels or functions (Studies to document outcome-measure utility should also demonstrate feasibility of including them in clinical trials.);
- Continuing to develop patient-reported outcome measures (PROs) suitable for use in specific muscle diseases by designing them with input from patients or by validating PROs developed for other diseases or conditions in people who have muscle diseases;
- Using new biomarkers to facilitate disease diagnosis so that treatments to slow or halt disease progression can be started early when they are most helpful;
- Establishing cost-effective methods of diagnosing muscle diseases (A precise molecular diagnosis (i.e., exact information on the nature of the mutation) is essential for many potential therapies moving into clinical trials.);
- Integrating biomarker data into databases that include standardized, common data elements to facilitate comparisons between the biomarkers and physical functioning and clinical outcomes within the study and across other studies;
- Conducting additional natural-history studies to characterize patient phenotypic variations, disease course, and comorbid conditions – especially for diseases that have not been previously studied this way. (Determine disease milestones that can be included in clinical trials of interventions that may block or reverse pathologies);
- Investigating genetic determinants of muscle mass and strength, efficient muscle repair, susceptibility to atrophy or disease, and treatment response (These data can provide a foundation for developing personalized medicines. Although many muscle diseases result from single-gene defects, GWAS offer opportunities to

clarify the genetic underpinnings of differences in disease manifestations and treatment responses);
- Studying environmental factors that may contribute to muscle diseases such as inflammatory myopathies and mechanisms by which these factors interact with genetic variants and gene products;
- Generating clinical patient data that will stimulate the development and testing of hypotheses related to disease pathophysiology;
- Evaluating patient transition to independence, level of care, and access to care, and use these data to inform hypotheses related to burden of disease and quality of health services;
- Determining incidence and prevalence of muscle diseases in racial and ethnic groups; and
- Exploring how care of patients with muscle diseases is affected by socioeconomic factors, geographic locations, and other demographic variables.

2. Clinical trials for muscle diseases

Numerous treatments of muscle diseases have demonstrated efficacy in animal models. Efficient testing of these promising interventions in humans are necessary for the development of effective treatments for various muscle diseases.

Broad areas of potential research directions include:

- Developing plans for clinical trials based on strong, reproducible data from animal studies or previous studies in humans;
- Conducting trials that test drugs, biologics, cell or gene therapies, molecular therapies, exercise regimens, or biomechanical or behavioral interventions that have potential to significantly advance muscle-disease treatments;
- Testing for additive or synergistic effects among interventions that have demonstrated efficacy potential;
- Combining knowledge gained through natural-history studies and innovative trial designs to increase the likelihood of trials reaching clear conclusions, while minimizing the required number of research participants;
- Designing clinical trials with outcome measures capable of following patients over the course of a disease so that both ambulatory and non-ambulatory patients can be included in the trial;
- Developing strategies to lessen the burden of study participation on patients and family members;
- Standardizing outcome measures to allow for treatment comparisons addressed in different studies;

- Determining how interventions such as nutrition, exercise, and physical therapy work (Such knowledge may lead to better treatments and improved compliance.);
- Developing and testing specialized exercise “prescriptions” to maintain function or restore health (Even if a therapy such as exercise or stretching has only modest effects on symptoms, it could make a meaningful difference in an individual’s life if combined with other interventions);
- Conducting trials with the highest likelihood of success first and developing strategies for managing patient participation in multiple trials, when possible (Consider patients as a rate-limiting resource for clinical trials in rare muscle diseases.);
- Using predictive biomarkers and data on genetic modifiers to select for and stratify trial participants to increase the likelihood of collecting conclusive clinical trial results;.
- Pursuing pharmacogenomic testing strategies that will allow personalized care with optimal treatment regimens; and
- In addition to testing interventions that address disease pathophysiology, conducting trials with behavioral interventions that address health-services outcomes and daily-living issues in people with muscle diseases.

LOOKING FORWARD

The NIAMS Long-Range Plan for FY 2015-2019 guides the Institute in its long-range planning, while enabling course corrections that are necessary due to the highly dynamic nature of modern biomedical and behavioral research. This Plan benefited from "the wisdom of the crowd," incorporating the suggestions and vantage points of investigators, health-care providers, patients, and patient advocates.

NIAMS remains committed to harnessing the best ideas from investigator-initiated research project grants and research conducted by early-stage scientists. The Institute also recognizes that 21st century biomedicine is catalyzed by state-of-the-art tools that are costly but extremely powerful. Thus, encouraging infrastructure- and data-sharing is a key strategy.

As part of a larger system, NIAMS will continue to establish and maintain partnerships with other NIH components, Federal agencies, foundations, and private-sector organizations to advance understanding, diagnosis, treatment, and, ultimately, prevention of arthritis and musculoskeletal and skin diseases. Through thoughtful planning and rigorous research, NIAMS will deliver on its promise to improve the quality of life of all Americans affected by diseases and conditions of the bones, joints, muscles, and skin.

APPENDICES

APPENDIX 1: OVERVIEW OF THE DEVELOPMENT PROCESS

The FY 2015-2019 NIAMS Long-Range Plan follows the same structure as the FY 2010-2014 plan, with cross-cutting sections and disease- and tissue-specific topics. The FY 2014-2018 Strategic Plan for the Office of Disease Prevention (https://prevention.nih.gov/sites/default/files/documents/ODP-StrategicPlan2014-2018.pdf), the NIH Strategic Plan for Women's Health Research (https://orwh.od.nih.gov/about/trans-nih-strategic-plan-womens-health-research), and the soon-to-be released Action Plan for the Muscular Dystrophies (to be posted at http://www.ninds.nih.gov/about_ninds/groups/mdcc/) will serve as companion pieces to the NIAMS Long-Range Plan for FY 2015-2019, since the needs and opportunities presented in these documents are of particular interest to the NIAMS and other NIH components. In addition, NIAMS will continue to partner with other NIH ICs with common research interests. An NIH-wide list of strategic plans can be found at: http://report.nih.gov/strategicplans/index.aspx.

NIAMS solicited comments on how the current long-range plan should be updated via a Request for Information (RFI) (Appendix 2) and gathered additional information through listening sessions with the NIAMS stakeholder community.

The RFI was posted on the NIAMS website and in the NIH Guide for Grants and Contracts, and it encouraged feedback from researchers, professional and patient advocacy organizations, health care providers, and patients and their families. The comment period spanned 90 days. Respondents were asked to provide input on research needs and opportunities that should be modified because of progress over the last five years, and emerging research needs and opportunities that should be added. General comments were also encouraged. A total of 68 responses were received through the RFI, with many responses consisting of more than one comment.

During December 2013, a series of six listening sessions were held with 80 individuals consisting of researchers and patients representing arthritis and rheumatic diseases, skin biology and diseases, bone biology and diseases, musculoskeletal biology and diseases, and muscle biology and diseases. Participants were encouraged to gather and share the views of the broader research community by consulting a diverse set of colleagues in advance of the listening sessions. In addition to providing input on their tissue- or disease-specific topic, participants were asked about needs and opportunities that could be included in the cross-cutting sections of this Plan on health disparities and training and career development. Five of the listening sessions were held via conference calls. The sixth session was an in-person meeting with K award mentors attending the NIAMS K Forum for Clinical Mentored K Awardees.

Another component of the NIAMS planning process includes yearly roundtable discussions, as well as an annual extramural program scientific retreat. Summaries of these meetings are posted on the NIAMS website and information was included in the Plan where appropriate. See Roundtables and Scientific Retreats.

Updates on the progress of the NIAMS Long-Range Plan for FY 2015-2019 were provided at the September 2013 and February 2014 Advisory Council meetings, and the draft plan was presented in June 2014. Additionally, in November 2013, the Institute provided a session at the NIAMS Coalition Outreach and Education Day on the purpose of the NIAMS Long-Range Plan, the process and timeline for revising the Plan, and details on how organizations could be involved. The NIAMS Coalition is a group of over 90 professional and voluntary organizations interested in the Institute's mission areas.

The draft Plan was posted on the NIAMS website for 38 days and comments were solicited via an RFI published in the NIH Guide for Grants and Contracts (Appendix 2). All comments were reviewed carefully by Institute staff and incorporated into the document, as appropriate.

After clearance by the NIAMS Advisory Council in September 2014, the final version of the NIAMS Long-Range Plan for FY 2015-2019 was posted on the Institute's public website and widely disseminated to NIAMS communities.

APPENDIX 2: REQUESTS FOR INFORMATION PUBLISHED IN THE NIH GUIDE FOR GRANTS AND CONTRACTS

Request for Information (RFI) on the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Long-Range Plan for Fiscal Year's (FY) 2015-2019

Notice Number: NOT-AR-14-010

Update: The following update relating to this announcement has been issued:

- November 19, 2013 - See Notice NOT-AR-14-011. Notice of Extension of the Expiration Date.

Key Dates
Release Date: October 18, 2013
Response Date: (Extended to **January 15, 2014** per NOT-AR-14-011) Originally December 15, 2013

Related Announcements
None

Issued by
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Purpose

Background

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is updating its Long-Range Plan to help guide the research it supports over the next five years. Public input on the topics to be included in the plan and suggestions regarding how to enhance the NIAMS research portfolio are critical initial steps in this effort. NIAMS leadership and staff will review and consider the comments as the Institute updates its Long-Range Plan.

Information Requested

Through this RFI, NIAMS invites feedback from researchers in academia and industry, health care professionals, patient advocates and health advocacy organizations, scientific or professional organizations, Federal agencies, and other interested members of the public. Organizations are strongly encouraged to submit a

single response that reflects the views of their organization and membership as a whole.

Please provide your perspective on the following issues as they relate to the NIAMS Long-Range Plan for Fiscal Years (FY) 2010-2014:

- Research needs and opportunities that should be modified because of progress over the past five years.
- Emerging research needs and opportunities that should be added to the plan.

NIAMS also welcomes your general comments, including those regarding the extent to which the FY 2010-2014 Plan has guided and encouraged the field.

When commenting on a research need or opportunity, your comments can contain but are not limited to information pertaining to the following:

- **Description of the opportunity**: Addressing an existing component of the FY 2010-2014 Plan that should be modified due to progress over the past five years, or a new opportunity for research not covered in the FY 2010-2014 Plan.
- **Rationale**: The scientific evidence or clinical basis for the proposed change or addition and the anticipated impacts that accomplishments or advances related to this issue would have on the scientific community and human health.

How to Respond

Responses to this RFI must be submitted electronically using the web-based format at [NIAMS is no longer accepting responses]. Responses will be accepted until December 15, 2013.

Responses to this RFI are voluntary. Please do not include any personally identifiable or other information that you do not wish to make public. Proprietary, classified, confidential, or sensitive information should not be included in your response.

This request is for information and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the United States Government. Neither NIAMS nor NIH will make any awards based on responses to this RFI, nor will NIAMS or NIH otherwise pay for the preparation of any information submitted or for the Government's use of such information.

NIAMS will use the information submitted in response to this RFI at its discretion and will not provide comments to any responder's submission. Respondents are advised that the Government is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted. The Government reserves the right to use any non-proprietary technical information in any resultant solicitation(s).

Inquiries
Please direct all inquiries to:

David S. Zielinski, Ph.D. Office of Science Policy, Planning and Communications
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Telephone: 301-496-8271
Email: niamslrpfeedback@mail.nih.gov

Request for Information (RFI) on the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Long-Range Plan for Fiscal Years (FY) 2015-2019

Notice Number: NOT-AR-14-020

Key Dates
Release Date: June 24, 2014
Response Date: July 31, 2014

Related Announcements
NOT-AR-14-010
NOT-AR-14-011

Issued by
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Purpose

Background

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has updated its Long-Range Plan to help guide the research it supports over the next five years. The Institute solicited initial comments on how the long-range plan should

be updated via a Request for Information (NOT-AR-14-010) and gathered additional input through listening sessions with the community.

The previous RFI was posted on the NIAMS website and in the NIH Guide for Grants and Contracts, and encouraged feedback from researchers, professional and patient advocacy organizations, health care providers, and patients and their families. The comment period spanned 90 days. Respondents were asked to provide input on the research needs and opportunities that should be modified because of progress over the last five years, and emerging research needs and opportunities that should be added to the Long-Range Plan. General comments were also encouraged. A total of 68 responses were received through the RFI, with many of the responses consisting of more than one comment. NIAMS leadership and staff reviewed and considered all of the input when preparing the Institute's draft Long-Range Plan for Fiscal Years (FY) 2015-2019. NIAMS also solicited input via listening sessions and the annual roundtables.

Information about the Institute's annual planning process can be found at the Roundtables page and the Scientific Retreats page.

Information Requested

Through this RFI, NIAMS invites feedback from researchers in academia and industry, health care professionals, patient advocates, representatives of health advocacy organizations, members of scientific or professional organizations, and other interested members of the public on the draft NIAMS Long-Range Plan for FY 2015-2019. Organizations are strongly encouraged to submit a single response that reflects the views of their organization and membership as a whole.

Please provide your comments and feedback. The final Long-Range Plan will be presented at the September 2014 meeting of the NIAMS Advisory Council and posted on the NIAMS website.

How to Respond

Responses to this RFI must be submitted electronically using the web-based form at [NIAMS is no longer accepting responses to this RFI]. Responses will be accepted until July 31, 2014.

Responses to this RFI are voluntary. Please do not include any personally identifiable or other information that you do not wish to make public. Proprietary, classified, confidential, or sensitive information should not be included in your response.

This request is for information and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the United States Government. The NIAMS or the NIH will not make any awards based on responses to this RFI, nor will the NIAMS or the NIH otherwise pay for the preparation of any information submitted or for the Government's use of such information.

The NIAMS will use the information submitted in response to this RFI at its discretion and will not provide comments to any responder's submission. Respondents are advised that the Government is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted. The Government reserves the right to use any non-proprietary technical information in any resultant solicitation(s).

Inquiries
Please direct all inquiries to:

Anita M. Linde, M.P.P.
Director, Office of Science Policy, Planning and Communications
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Telephone: 301-496-8190
Email: lindea@mail.nih.gov

APPENDIX 3: DEVELOPMENT TIMELINE FOR THE NIAMS LONG-RANGE PLAN: FISCAL YEARS 2015-2019

2013	September	Update to NIAMS Advisory Council on the development of the Plan.
	October	Request for Information posted in the NIH Guide for Grants and Contracts and on the NIAMS website for public input on research needs and opportunities that should be modified because of progress over the last 5 years and emerging research needs and opportunities.
	November	Update to NIAMS Coalition on the development of the Plan.
	December	Listening sessions held as conference calls for: • arthritis and rheumatic diseases • skin biology and diseases • bone biology and diseases • muscle biology and diseases • musculoskeletal biology and diseases Listening session with participants at the NIAMS Forum for Clinical Mentored K Awardees
2014	February	Update to NIAMS Advisory Council on the development of the Plan.
	June/July	• Draft plan presented to NIAMS Advisory Council for review and input. • Draft plan presented to NIAMS Coalition for review and input. • Draft plan and a Request for Information posted in the NIH Guide and on the NIAMS website to gather public input.
	August	Review of public comments on draft Plan and updates incorporated, as appropriate.
	September	Final Plan presented to NIAMS Advisory Council and posted on the Institute's website.