National Institute of
Arthritis and Musculoskeletal
and Skin Diseases

Strategic Plan
Fiscal Years 2020-2024

Turning Discovery Into Health

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DIRECTOR'S MESSAGE

Promoting the Unexpected

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is pleased to present its Fiscal Years 2020-2024 Strategic Plan. The fields that NIAMS supports have seen major advances in recent years and are now poised for additional rapid progress. Therefore, the NIAMS Strategic Plan conveys both the tremendous potential of the current research trajectory and the Institute's aspirational vision for how work over the next 5 years may lead to meaningful improvements in human health.

Mission

The NIAMS mission is to support research into the 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.

Importantly, this plan is not intended to be a rigid roadmap for investigators to follow. While we will continue to invest in various well-defined areas, we will also seek to foster a rich and adaptable research environment that enables scientists to capitalize on opportunities as they arise. By putting structures in place to identify, promote, and support advances that we cannot predict at the present, we hope to stimulate new areas that are unexpected and transformative. Thus, this Plan for the next 5 years should be viewed not as directions to a defined destination, but rather as a point of departure for exploration to spark unanticipated discoveries.

Goal

The goal of the plan is to advance and accelerate research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. The ultimate goal of these efforts is to develop patient-centered, personalized ways to improve outcomes and thereby "turn discovery into health."

This strategy of promoting the unexpected has important implications for priority setting. First, NIAMS must look to the research community for new ideas, rather than prescribing what gets done. Second, it requires maintenance of a broad base of researchers. Third, funding must be based on new and promising ideas and not just on past performance. Therefore, we will continue to value and support the best ideas proposed in investigator-initiated research project grants. Simultaneously, NIAMS must be poised to embrace unexpected opportunities for collaborations with other NIH components, advocacy organizations, and industry to fund larger scale, team science approaches, such as the Osteoarthritis Initiative, the

Accelerating Medicines Partnership, the Molecular Transducers of Physical Activity Consortium, and the NIH Back Pain Consortium Research Program.

To support this strategy, the Strategic Plan describes potential research areas of interest over the next 5 years. Although it is not possible to reference every disease or condition within our broad portfolio, it covers the following five research objectives related to the core tissue- and disease-specific areas within the NIAMS mission, namely, advancing and accelerating:

- Systemic rheumatic and autoimmune diseases research;
- Skin biology and diseases research;
- Bone biology and diseases research;
- Muscle biology and diseases research; and
- Joint biology, diseases, and orthopaedics research.

Each of the sections devoted to the five objectives features a major project or activity to highlight a significant NIAMS accomplishment in that area. A number of these highlighted projects also showcase the Institute's leadership in collaborative activities to advance science. Leveraging partnerships has been a major strength of NIAMS, and we will continue to pursue this strategy to accomplish our research objectives.

Aspirations

Looking across the NIAMS portfolio, many reasons exist to be hopeful. Progress related to the cross-cutting themes is relevant to several diseases and conditions within the NIAMS mission.

The new plan differs from previous NIAMS planning documents in two ways. First, it features four broad cross-cutting scientific themes that are relevant to all, or most, of the disease- and tissue-specific topics within the NIAMS mission. We chose these themes because they were heard across the "listening sessions" we held with representatives from each of our research areas. As such, research topics included in this section also appear throughout the disease- and tissue-specific sections both to provide additional detail in each of the areas and to ensure that these key points reach all audiences. These themes, which provide potential opportunities to better organize and conduct science across our mission areas, are:

- Precision medicine for arthritis and musculoskeletal and skin diseases;
- Shared mechanisms in health and among diseases;
- Patient-centric approaches to health and disease; and
- Health and disease in diverse populations.

The themes focus on the increasing convergence of scientific knowledge and approaches across fields, which represents an unprecedented opportunity to invigorate the conduct of science. To

illustrate the potential of these areas, we have included several aspirations that provide examples of a vision for where cross-cutting, convergent research may lead us in the coming years or decades. Although NIAMS primarily funds individual investigator-initiated research projects, we encourage investigators to consider convergence with other scientific areas as they plan their own research and, when possible, to collaborate across disciplines.

Second, the plan includes a new section that addresses National Institutes of Health (NIH) and NIAMS activities related to:

- Priority setting;
- Workforce recruitment, development, retention, and diversity;
- Innovation;
- Research partnerships;
- Inclusion of diverse populations as participants in biomedical research;
- Performance measures and assessment; and
- Information dissemination and outreach.

Including these topics in our Strategic Plan is a key step in sharing information with the research community and the public about our commitment to responsible management, stewardship, and accountability. Over the next 5 years we will continue to support and promote these initiatives while looking for additional opportunities to be even more transparent about the Institute's efforts in these areas.

Importantly, the development of this plan benefitted from the collective wisdom of members of both the scientific and lay communities interested in and affected by diseases and conditions within the NIAMS mission, and we thank all those who contributed their expertise and insights. We hope that the Fiscal Years 2020-2024 Strategic Plan will inspire those involved or interested in NIAMS research as investigators, research participants, patients, or the general public, and that it serves as a resource for all who have an interest in our mission. We encourage you to share the plan broadly with your colleagues.

/Robert H. Carter/
Robert H. Carter, M.D.
Acting Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health

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 NIAMS mission is to support research into the 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.

The Institute's research portfolio includes five core mission areas: (1) Systemic Rheumatic and Autoimmune Diseases; (2) Skin Biology and Diseases; (3) Bone Biology and Diseases; (4) Muscle Biology and Diseases; and (5) Joint Biology, Diseases, and Orthopaedics. Within these mission areas, NIAMS supports research at multiple levels, ranging from basic studies to enable comprehensive understanding of the molecular mechanisms underlying disease processes to preclinical research in model systems to translational studies to clinical and epidemiological research. In addition to research projects, NIAMS supports research training and career development, scientific conferences, and research infrastructure such as core facilities that enhance and accelerate NIH-funded research or research that is sponsored by other public and private organizations. The ultimate goal of these efforts is to develop patient-centered, personalized ways to improve outcomes and thereby "turn discovery into health."

The NIAMS Strategic Plan for Fiscal Years (FYs) 2020-2024 is a part of the Institute's scientific planning process. The goal of the plan is to advance and accelerate research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. 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 policymakers—about needs and opportunities related to the NIAMS mission. The plan is not intended to prescribe what investigators should pursue in their exploration of scientific problems that bear on the health of bones, joints, muscles, and skin. Rather, it is intended as a guide that might lead to unanticipated new scientific directions. As always, the Institute will continue to value and rely on investigator-initiated science as a critical source of innovation.

Cross-cutting scientific themes

Although the plan includes research objectives related to the Institute's five disease- or tissue-specific areas noted above, modern biomedical and behavioral research increasingly crosses those traditional disease- and tissue-specific boundaries. Many scientific challenges and opportunities within the NIAMS mission are not unique to any one field, disease, or scientific or clinical discipline. Therefore, the FYs 2020-2024 plan includes a new section highlighting cross-cutting scientific themes relevant to many areas of the NIAMS mission. These themes, briefly outlined below, provide a framework for understanding the convergence of ideas, knowledge, and approaches across fields.

Precision medicine for arthritis and musculoskeletal and skin diseases

Emerging technologies, such as techniques to analyze single cells and innovative genomic approaches, have yielded a wealth of data that can be integrated with clinical information to build sophisticated new models of health and disease. In the coming years, these approaches, which give researchers powerful new tools to address longstanding research questions, are expected to advance knowledge in many NIAMS mission areas and yield more personalized treatments for patients.

Shared mechanisms in health and among diseases

Increasingly, researchers are discovering commonalities among seemingly disparate diseases and revealing how basic processes such as immunity, inflammation, regeneration, and metabolism play a role in maintaining health or, when perturbed, in the development of disease. The discovery of shared molecular, physiological, and behavioral components and mechanisms of action across different diseases is blurring the traditional boundaries of biomedical science and challenging investigators to employ new approaches to explore scientific questions.

Patient-centric approaches to health and disease

Over the past 5 years, efforts to integrate the patient perspective into research have progressed. New tools are available to capture patient-reported data for use in clinical trials and care. This integration offers promise for more holistic therapies to improve health and enhance the patient experience.

Health and disease in diverse populations

Different demographic groups often have distinct health concerns and disparities exist among groups with regard to health outcomes for diseases within the NIAMS mission. To achieve the

goal of improving human health, NIAMS-funded research must be applicable to health and disease in many populations.

Management, scientific stewardship, and accountability

In addition to the new focus on the cross-cutting scientific themes described above, the plan also includes a section dedicated to the Institute's commitment to managing, accounting for, and providing stewardship of the public resources that support its mission. This component of the plan describes the ways in which NIAMS sets priorities and invests taxpayer funds strategically. Through various activities, NIAMS fosters the next generation of researchers in NIAMS mission areas, supports investigation of bold and innovative hypotheses, encourages the development and sharing of state-of-the-art resources, ensures the inclusion of diverse populations in biomedical research, and provides information to the public about NIAMS-funded scientific advances. Specific topics related to this commitment include the following.

Priority setting

NIAMS employs a standard process for making funding decisions, the cornerstone of which is peer review by the research community coupled with careful consideration by Institute leadership. This process helps to ensure that the Institute invests in highly meritorious research that addresses promising scientific opportunities and pressing public health needs.

Workforce recruitment, development, retention, and diversity

Biomedical and behavioral research is a human endeavor and NIAMS is committed to keeping the talent pipeline robust and diverse. Fostering early-stage investigators and supporting a range of research training and career development programs for mid-career clinicians and scientists are key NIAMS goals.

Innovation

New and highly innovative hypotheses and approaches play important roles in moving science forward. Although exploring such hypotheses may entail higher risk than pursuing research that builds incrementally, highly novel research has tremendous potential to advance scientific knowledge and expand technological capabilities. In addition to supporting trans-NIH efforts to foster innovation, NIAMS supports targeted initiatives to encourage paradigm-shifting research in its mission areas.

Research partnerships

NIAMS works closely with other NIH components to advance research in areas of shared interest. Through participation in trans-NIH working groups the Institute ensures that diseases within its purview are included in trans-NIH initiatives and avoids duplication of effort with other NIH entities. Like all NIH Institutes, Centers, and Offices, 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 across NIH to support cross-cutting research and address infrastructure needs not unique to any given NIH component. 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 numerous scientific areas in ways that it would be unable to tackle alone.

Inclusion of diverse populations as participants in biomedical research

NIAMS supports research to improve understanding about the unique health needs of women, children, older adults, minorities, and other groups and to address health disparities. This research is supported by tangible polices to ensure that women, racial/ethnic groups, and other populations are included as participants in NIAMS-funded clinical research. In addition, the Institute supports NIH-wide efforts to incorporate sex as a biological variable in preclinical research.

Performance measures and assessment

NIAMS uses quantitative and qualitative approaches to inform the development, conduct, and improvement of Institute programs. Through these careful assessments, the Institute enhances its efforts to further the ultimate goal of turning discovery into health.

Information dissemination and outreach

To maximize return on its investment in research, NIAMS encourages the dissemination of research findings to health care providers and the public. NIAMS will continue working closely with stakeholders to promote broad dissemination of scientific and health-related knowledge to the Institute's varied communities.

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Importantly, the NIAMS Strategic Plan for FYs 2020-2024 is a starting point, not a destination. While the plan is intended to provide a broad view of potential opportunities and challenges, research is likely to advance and evolve in many unanticipated ways over the 5-year period. The

Institute is committed to communicating transparently with its stakeholders about its future plans to maximize the careful stewardship of federal funds and to respond appropriately to emerging needs and opportunities in science and health.

INTRODUCTION, MISSION, AND STRUCTURE

Introduction

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 over time. The NIAMS Strategic Plan for FYs 2020-2024 will facilitate communication between the Institute and its many constituents—scientific communities, health care providers, health advocacy organizations, the general public, and policymakers—about needs and opportunities related to the NIAMS mission.

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. Most of the diseases covered by the NIAMS mission areas are chronic and many cause lifelong pain, disability, or disfigurement. Diseases within the NIAMS mission also may lead to or be associated with the development of other serious medical conditions, referred to as comorbidities or co-occurring conditions. Some of these conditions are very common, while some are rare, affecting only a few thousand people worldwide. The 2017 Global Burden of Disease data have provided a wealth of information about the extent to which many of these conditions affect society. For example, in 2017, low back pain was the leading cause of disability in the United States, as measured in years lived with disability (YLDs).[1] Other musculoskeletal diseases, a category that includes many systemic rheumatic, bone, muscle, and joint diseases, was among the top 10 causes of YLDs. The Centers for Disease Control and Prevention (CDC) estimate that 57.9 million adults in the United States have arthritis,[2] and a recent study suggests that this may be an underestimate.[3] As the U.S. population ages, the prevalence of arthritis and its associated costs is expected to grow.

[1] The Institute for Health Metrics and Evaluation (IHME). (2017). United States. Available at http://www.healthdata.org/united-states

[2] Centers for Disease Control and Prevention (CDC). National Center for Health Statistics. (2017). Arthritis. Available at https://www.cdc.gov/nchs/fastats/arthritis.htm

[3] Jafarzadeh SR, et al. *Arthritis Rheumatol*. 2018. PMID: 29178176.

Whether common or rare, many diseases and conditions within the NIAMS mission affect women and minorities disproportionately, both in increased numbers of those affected and increased disease severity. For example, findings from recent CDC-funded population-based systemic lupus erythematosus (SLE) registries in Alaska, California, Georgia, Michigan, and New York provide additional information about lupus health disparities. These and earlier studies show that women with SLE significantly outnumber men, and the disease is more common in African American, Hispanic, Asian, and American Indian women than in white women.[4] Furthermore, the CDC-funded research documents an earlier onset of lupus and higher burden of disease in African Americans than in whites.[5] [6] 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 factors play can inform the development of strategies to reduce outcome disparities, and that knowledge will enable early diagnosis and disease management tailored to an individual's needs.

In accordance with the 21st Century Cures Act (Public Law 114-255), enacted in 2016, the NIAMS Director consults with the Director of the National Institute on Minority Health and Health Disparities (NIMHD) and the Director of the Office of Research on Women's Health (ORWH) regarding NIAMS objectives to ensure its future activities take into account the health needs of women and minorities and are focused on reducing health disparities. NIAMS works closely with NIMHD and ORWH, and NIAMS staff are active participants in standing and ad hoc committees related to NIH priorities for women's health, minority health, and health disparities. These relationships enable the Institute to align its work in these areas with broader NIH efforts and to leverage and synergize with related activities across NIH.

The goal of the NIAMS FYs 2020-2024 strategic plan is to advance and accelerate research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. Like the previous plans, it is expected to continue to promote exploration of ideas and encourage new research directions as needed. Although NIAMS expects to continue to devote the majority of its extramural budget to funding the most meritorious investigator-initiated research, 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 stimulate

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[4] CDC. (2018). Lupus. Available at https://www.cdc.gov/lupus/funded/lupus-studies.htm
[5] Somers EC, et al. *Arthritis Rheumatol*. 2014. PMID: 24504809.
[6] Lim SS, et al. *Arthritis Rheumatol*. 2014. PMID: 24504808.

research progress related to improved understanding, diagnosis, treatment, and ultimately prevention of diseases within the NIAMS mission.

The plan is not meant to be comprehensive; it does not mention every research area or disease of interest by name. As a broad scientific outline for NIAMS, however, it elaborates some of the Institute's known areas of interest, while enabling the Institute to adapt to rapidly changing biomedical and behavioral science landscapes.

Mission and Statutory Authority

The Health Research Extension Act of 1985 (Public Law 99-158) authorized the establishment of NIAMS, which was formally established in 1986. The mission of NIAMS is to support research into the 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.

NIAMS Organizational Structure

NIAMS is one of 27 Institutes and Centers of NIH, the Nation's premier biomedical research agency. NIH is the steward of medical and behavioral research for the Nation. The agency is responsible to Congress and the U.S. taxpayers for carrying out its mission to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability, in a manner that not only facilitates research but does so cost-effectively and in compliance with applicable rules and regulations.

The NIAMS organizational structure includes an Office of the Director, which provides overall leadership for and administration of the Institute's components, including the Division of Extramural Research (DER) and the Intramural Research Program (IRP). The NIAMS DER supports scientific studies and research training and career development throughout the country through grants and contracts to research organizations. The NIAMS IRP, located on the NIH campus in Bethesda, Maryland, conducts high-risk, high-reward basic, translational, and clinical research in NIAMS mission areas.

The NIAMS Strategic Plan for FYs 2020-2024 focuses primarily on the Institute's extramural program because the NIAMS intramural strategic planning process is linked to a larger NIH-wide planning process for intramural research. Furthermore, the NIAMS IRP has a number of capabilities and resources that are purposefully different from, and complementary to, those supported by the NIAMS DER. The science conducted by the IRP has a more restricted focus than that of extramural research in part because of budgetary limitations, but also to focus on the

unique strengths of the IRP. For example, the IRP has a long tradition of excellence in long-term, high-risk research into the genetics and pathophysiology of human disease and the development of innovative therapies for a number of serious disorders for which satisfactory treatments previously did not exist. The IRP also has several distinctive characteristics, including: a unique funding model using a largely retrospective review of investigators to inform funding decisions; a concentration of interactive outstanding investigators in a collaborative environment with fluid boundaries between basic, translational, and clinical research; exceptional research resources, including the NIH Clinical Center; a longstanding culture of mentoring trainees at all levels; and a rich environment for training physician-scientists due to the presence of basic, translational, and clinical researchers.

CROSS-CUTTING SCIENTIFIC THEMES

Many scientific challenges and opportunities within the NIAMS mission are not unique to any one field, disease, or scientific or clinical discipline. Rather, they transcend disease- and tissue-specific boundaries, have broad impact across many diseases and conditions, and can therefore serve as a framework to organize science across the assorted fields within the Institute's purview. A commonality that links these themes is the concept of convergence science, which refers to the coming together of different scientific and technological fields to catalyze scientific progress. This section of the Strategic Plan describes the following four cross-cutting scientific themes:

- Precision medicine for arthritis and musculoskeletal and skin diseases
- Shared mechanisms in health and among diseases
- Patient-centric approaches to health and disease
- Health and disease in diverse populations

Because they are cross-cutting, these themes resonate and create synergies with the scientific goals described in the disease- and tissue-specific sections of the plan. Many of the research areas described under these themes are addressed with greater specificity within those sections, depending on the stage of development of the field. For example, microbiome studies focus on mechanisms and effects of multiple microorganisms that are shared across many areas of health and disease, but such studies are more advanced in skin research than in many other areas.

The cross-cutting scientific themes represent areas that might benefit from an overarching approach, for example, the development of multi- and interdisciplinary teams to advance research on tissue interactions. In some cases, they highlight a collective need across mission areas for shared complex technologies, for example, in vivo visualization of molecules or cells. They are often areas for which multiple diseases require the same methodological approach, such as extensive phenotyping to better characterize disease heterogeneity. They also reveal emerging scientific opportunities such as improved understanding of environmental triggers of disease initiation and progression.

NIAMS Aspirations

Looking across the NIAMS portfolio, many reasons exist to be hopeful. The list below provides a few examples of advances that are possible during the next 5 years. These aspirations exemplify the broad concepts, for example, precision medicine, described under the cross-cutting themes. Importantly, this list is neither comprehensive nor exhaustive. Progress related to the cross-cutting themes is relevant to several diseases and conditions within the NIAMS mission. In addition, many unanticipated advances in a range of areas are likely to occur. Although unable to guarantee that all of these aspirations will be realized, these are areas in which the state of the science suggests a clear path forward. They are intended to convey the promise of the science and a vision for improving health and quality of life.

- ✓ A gene therapy for muscular dystrophy or epidermolysis bullosa will restore the function of the missing or mutated gene and improve patient outcomes.
- ✓ Biomarkers will guide the choice of the most effective therapy for each individual rheumatoid arthritis patient.
- ✓ New nonsurgical treatments, including medical or regenerative medicine therapies, will be available to reduce pain and disability in patients with osteoarthritis.
- ✓ Preventive therapy will delay the onset of autoimmune diseases like lupus and rheumatoid arthritis.
- ✓ New personalized nonaddictive therapies will reduce chronic low back pain.
- ✓ Clinical research will demonstrate the efficacy of intervention(s) to reduce disparities between minority populations and the general population in access to and use of existing surgical and nonsurgical interventions for osteoarthritis.
- ✓ The number of fractures due to osteoporosis will decline as precision medicine allows treatment to be targeted based on the specific mechanism of bone loss occurring in a particular patient.

Precision Medicine for Arthritis and Musculoskeletal and Skin Diseases

The emergence of powerful new technologies and computational tools to measure and analyze biological mechanisms has advanced our understanding of the molecular basis of health and disease. These tools also present unique opportunities to realize the promise of precision medicine, that is, treatment targeted to an individual's unique biology. Integrating multifaceted disease mechanism data with accurate and detailed clinical and patient-reported information offers new possibilities for understanding variations in symptoms, co-occurring conditions, and response to therapy among patients with the same diagnosis, and for precise targeting of disease pathways active in different patients. This integrated information could be used to identify

patient subsets, inform the development of new therapies, tailor the specific range of drugs now available to individual patients, and enhance risk-benefit assessments**.**

Focus areas

"Omics" at the tissue and single cell levels

- Enhancing the use of multiple approaches to quantitation of genes, proteins, metabolites, and cellular and tissue pathways in physiologic and pathologic states
- Determining global sets of molecular interactions, that is, the interactome, in cell types of interest
- Promoting the application of advanced organ, tissue, and cellular structural and functional imaging technologies to collect data on normal and pathological states of tissues including bone, muscle, skin, and connective tissue

Precision medicine in clinical research and clinical care

- Applying "omics" to develop deep phenotyping[7] of arthritis and musculoskeletal and skin diseases to improve understanding of disease heterogeneity and identify disease subtypes
- Facilitating implementation and dissemination of deep phenotyping technologies and methods
- Improving understanding of adaptive mechanisms that may contribute to health by allowing secondary pathways to compensate for the loss of primary ones
- Leveraging natural history studies to determine the natural progression of disease and identify risk factors and markers of common and rare diseases within the NIAMS mission
- Using -omics approaches to enable the development of new diagnostic tools
- Enhancing the pipeline for development and validation of disease biomarkers and surrogate endpoints of disease
- Applying gene editing techniques (e.g., CRISPER-Cas9) to develop gene therapies for genetic diseases

[7] "Deep phenotyping can be defined as the precise and comprehensive analysis of phenotypic abnormalities in which the individual components of the phenotype are observed and described." See Robinson PN. *Hum Mutat*. 2012. PMID: 22504886

Data science, computational science, and artificial intelligence

- Aligning NIAMS efforts with strategies for managing big data included in the NIH Strategic Plan for Data Science, such as the FAIR (**f**indable, **a**ccessible, **i**nteroperable, and **r**eusable) data principles
- Capitalizing on NIH data science infrastructure, tools, and resources, such as the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) initiative to advance arthritis and musculoskeletal and skin diseases research
- Identifying key research challenges and opportunities that can be uniquely addressed by focused efforts in artificial intelligence and computational science
- Determining ways to enhance access to multidomain tissue and disease data

Shared Mechanisms in Health and Among Diseases

Several basic biological processes critical to maintaining or restoring health are common across dissimilar tissues and organ systems. For example, inflammatory, reparative, regenerative, and metabolic processes may be similar across tissues and are closely linked through the processes of immune system activation and stem cell stimulation. Sharing knowledge from research on one tissue system could inform investigations of others and lead to better understanding of the role of basic biological processes in promoting health or causing disease across a number of tissues. Because perturbations of these basic processes can lead to disease, comparisons among diseases could provide researchers with new insights into potential mechanisms and therapeutic targets.

Focus areas

Immunity and inflammation

- Understanding the role of immune cells in the maintenance of normal homeostasis in tissues, for example, skin, bone, connective tissue, and muscle
- Exploring the role of immune responses and inflammation in genetic and acquired diseases of skin, bone, joint, and muscle
- Investigating the role of inflammation in disease onset, progression, or recovery and healing in genetic and degenerative diseases of bone, joint, muscle, and skin
- Studying immune and inflammatory targets in the treatment of genetic and degenerative bone, joint, muscle, and skin diseases

Regenerative medicine: Wound healing, tissue repair, and regeneration

- Identifying common pathways involved in wound healing and tissue regeneration
- Dissecting repair and regeneration processes, including maladaptive repair responses like fibrosis and sclerosis
- Expanding research on stem cell therapy and other emerging approaches like platelet-rich plasma treatments for musculoskeletal injuries to provide a scientific basis for enhancing their effectiveness and safety
- Encouraging the use of multidisciplinary teams and integrative approaches to investigate cell-cell, tissue-tissue, and cell-extracellular matrix interactions critical to maintaining and restoring structure and function
- Advancing research on the biology of junctional tissues such as the enthesis and associated transitional areas between tissues to inform the development of clinical approaches and improve outcomes for diseases within the NIAMS mission

Neurosensory aspects, including pain and itch

- Identifying the relative contribution of nociceptive, neuropathic, and central pain and the role of itch mechanisms in chronic conditions and the shared and distinct pathways involved in pain and itch
- Exploring the relationship between pain, itch, and inflammation in both acute and chronic diseases within the mission of NIAMS
- Investigating the relationships among pain, itch, and function to understand how their intersections contribute to disability

Effects of environmental exposures

- Improving understanding of the role of the microbiome in normal tissue development and homeostasis and during disease and recovery
- Identifying chemical and physical exposures that may increase susceptibility to disease and understanding how these factors affect onset and severity of disease
- Enhancing research on the effects of nutrients, diet, and exercise on health and as adjuncts to treatment
- Studying gene-environment interactions

Metabolism

- Studying the roles of skin, muscle, bone, connective tissue, and the immune system in maintaining balanced body metabolic rates (homeostasis)
- Determining the metabolic pathways that affect cell proliferation, function, and senescence using technologies such as metabolomics, lipidomics, and glycomics

Patient-Centric Approaches to Health and Disease

Clinical research plays a vital role in translating basic knowledge into interventions to improve health. Researchers are developing innovative approaches to clinical research that incorporate existing patient data systems and other emerging resources. At the same time, there is growing recognition and awareness of the role of biopsychosocial factors as important contributors to both disease manifestations and responses to interventions. Careful analysis of patient characteristics as well as particular patterns of disease in a specific person (endotype), including patient-reported symptoms and preferences, will contribute to development of therapies personalized for the individual patient. The PROMIS® (Patient-Reported Outcomes Measurement Information System), described below, is an example of one tool to capture a patient's daily quality of life through self-reporting. Finally, including patients and their caregivers as partners in the design and implementation of research projects, including the development of research questions, directions, priorities, and outcome measures, will be critical to the success of efforts to improve the development and testing of new therapies.

Patient-Reported Outcome Measures: Incorporating the Patient Perspective

There are many ways to clinically measure a patient's health status, such as through blood tests and X-rays. However, these may not capture features that affect daily quality of life, such as pain and fatigue. To address the need to incorporate patient input into clinical research and care, NIH is advancing patient-reported outcome (PRO) measures. These efforts, including the Patient Reported Outcomes Measurement Information System (PROMIS®)[1], grew out of an NIH Common Fund initiative[2] administered by NIAMS. The initiative supported the development and validation of a wide range of psychometrically and clinically robust instruments to gather information on health-related concerns, such as pain, fatigue, and physical functioning, across a wide range of disorders in adults and children. PROMIS adult and pediatric measures are being adapted for use across numerous diseases, languages, literacy levels, and ethnic groups. Patients can report their information in a variety of settings, including by phone or online. Today, the tools are being used to assess symptoms and measure changes over time and in response to treatment in both clinical trials and patient care settings both nationally and internationally. The measures are helping to better tailor and monitor treatments and understand diseases and their

impact on patients' symptoms, functioning, and quality of life. NIAMS is encouraging the use of these tools to foster patient-centric care for diseases within its mission.

Although the original Common Fund initiative that spurred the development and validation of PROMIS and other PRO measures has ended, the program has successfully shifted to a sustained research effort supported by a trans-NIH cooperative agreement. Current work is advancing the science of PRO measures (PRO-omics) and facilitating their integration in complementary and meaningful ways with other 'omics' (e.g., transcriptomics) data that assess a person's disease and health status. Some of the available measures are designed to assess a specific disease or condition, while others, such as PROMIS, are applicable to many different conditions and can therefore be used to facilitate within or across disease comparisons.

PRO measures increasingly are being adopted for use in pediatric populations. For example, NIAMS administers the Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) consortium[3], an initiative that capitalizes on recent advances in PROMIS pediatric measures to assess the health of children with a variety of chronic diseases and conditions in clinical research and care settings. The PEPR tools are informing and supporting the NIH Environmental Influences on Child Health Outcomes Program[4] to capture the perspectives and experiences of children and their families who are participating in this groundbreaking pediatric consortium.

For further information see:

[1] The Patient Reported Outcomes Measurement Information System (PROMIS®) webpage.
[2] The Common Fund PROMIS® webpage.
[3] Information about the Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) consortium.
[4] The Environmental Influences on Child Health Outcomes Program website.

Focus areas

The patient experience

- Advancing the development, validation, and use of patient-reported outcomes in clinical trials and longitudinal studies within the NIAMS portfolio
- Promoting development and testing of measures, wearable devices, and biosensors to assess physical function and other outcomes
- Encouraging research on patient preferences to identify the most important benefits of interventions, understand barriers to implementing prevention and treatment approaches, provide evidence for risk/benefit assessments, and identify variability of preferences at the individual and population levels

- Using information about biological mechanisms to inform the development of individualized and multimodal diagnostic and treatment algorithms for pain management
- Improving understanding of biopsychosocial (e.g., sensory, cognitive, and affective) components of pain to understand the distinction between tissue damage and the experience of pain
- Promoting development and testing of approaches tailored to preventing or treating co-occurring conditions
- Advancing dissemination and implementation research and methods to encourage the application of evidence-based practices in health care settings
- Encouraging research that incorporates rehabilitation science, including patient-centered rehabilitation approaches, in the study of diseases and conditions within the NIAMS mission

Innovative approaches to clinical trials

- Encouraging the development of trials targeting preclinical disease to develop effective strategies for disease prevention
- Promoting the use of new methodologies, emerging research frameworks, and innovative resources, such as linking to the electronic medical record, in clinical studies to achieve greater efficiency and effectiveness
- Using molecular signatures and biomarkers to better stratify and classify patients for participation in clinical trials
- Leveraging clinical research resources, such as those in the Clinical and Translational Science Awards program, to test new trial designs
- Engaging key stakeholders in the health care provider and patient communities to enhance the application of trial results to medical practice
- Improving clinical trial design and recruitment to increase participation of populations of diverse ancestral backgrounds, including encouraging community-based participatory research and addressing barriers that discourage participation of diverse groups
- Facilitating natural history studies and observational studies to improve understanding of early disease processes, risk factors for disease, and disease transitions

Health and Disease in Diverse Populations

Research funded by the Institute is relevant to a number of populations, including groups historically underrepresented in biomedical research. NIAMS supports research to explore

biological, mechanistic, environmental, biopsychosocial, cultural, and other factors that affect the health of specific populations and how these factors may differ among groups, the interactions among these factors, and their potential contribution to health outcomes. The next 5 years offer exciting opportunities to develop interventions that could improve health and reduce health disparities. For example, the interface between patients and the health care system is emerging as an important area of research, and more is being learned about how an individual's background affects communication with health care providers, perception of the risks and benefits of treatments, and individual patient preferences. Ultimately, NIAMS-funded research seeks to provide evidence to achieve health equity for all populations.

Focus areas

Health research in diverse groups

- Pursuing research on diseases with significant effects on the overall health and quality of life of populations that have been underrepresented in biomedical research
- Investigating genetic, biological, and environmental mechanisms of disease in different racial, ethnic, and other underrepresented groups, as well as between the sexes and across the lifespan
- Studying the influence of social determinants of health in different populations
- Using novel methodologies to dissect the biological and biopsychosocial factors contributing to the observed greater prevalence in women of diseases like lupus and osteoporosis
- Expanding research to improve understanding of the causes and long-term consequences of chronic and genetic diseases in children

Health disparities research

- Investigating genetic, biological, and environmental mechanisms, as well as social determinants contributing to health disparities (e.g., greater susceptibility to or increased severity of disease)
- Exploring how health disparities may be related to symptom descriptions provided by patients, unconscious bias or lack of cultural competency of health care providers, or variability in treatment response
- Understanding how comorbid (co-occurring) conditions may contribute to health disparities
- Understanding how sex differences may contribute to health disparities between men and women in diseases of the bones, joints, muscles, and skin
- Expanding use of health care data sources, such as electronic medical records and administrative databases (e.g., billing and pharmacy) to study health disparities

Effective therapies across diverse populations

- Testing interventions to reduce health disparities by improving health in all populations
- Incorporating findings from behavioral research to develop effective patient education strategies to promote adoption of healthy behaviors among diverse groups
- Examining ways that treatment protocols and interactions with health care providers and systems could be modified to better serve diverse populations (e.g., to encourage the appropriate use of total joint replacement for all populations)
- Advancing dissemination and implementation research focused on improving the uptake of research findings in diverse communities to improve health

DISEASE- AND TISSUE-SPECIFIC SCIENTIFIC OBJECTIVES

The goal of the NIAMS FYs 2020-2024 strategic plan is to advance and accelerate research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. The plan includes five objectives to advance and accelerate:

- Systemic rheumatic and autoimmune diseases research;
- Skin biology and diseases research;
- Bone biology and diseases research;
- Muscle biology and diseases research, and
- Joint biology, diseases, and orthopaedics research.

The following sections describe NIAMS objectives in each of these five areas. These objectives focus on research to understand basic mechanisms of biological processes, investigations of the genetic and environmental causes of disease, preclinical research to translate new knowledge into potential therapies, and clinical research to assess the efficacy or new interventions. Research related to the objectives includes hypothesis-driven research as well as discovery research depending on the stage of the research field and ability of the scientific approach to shed light on a particular research question. Many topics described in the preceding section on cross-cutting scientific themes are addressed more comprehensively in these sections.

Although much of the arthritis and musculoskeletal and skin diseases research landscape falls within the NIAMS mission, some is included in the missions of other NIH components. In practice, the NIAMS collaborates closely with other NIH Institutes, Centers, and Offices in these areas of shared interest to achieve synergies and avoid duplication of effort. Research areas that clearly fall outside of the NIAMS mission (e.g., cancer) are generally not included in this strategic plan.

As part of NIH, NIAMS is focused on the discovery of new biological knowledge and its application to improve human health. NIAMS helps to generate the evidence needed to advance new and improve existing treatments. Because the agency's mission does not cover the entire healthcare continuum, the Institute works with partners in other Federal agencies, professional and patient groups, and industry to speed the translation of NIAMS-funded research.

Advancing and Accelerating Systemic Rheumatic and Autoimmune Diseases Research

NIAMS Systemic Rheumatic and Autoimmune Diseases programs address basic, translational, and clinical research, including clinical trials and observational and mechanistic studies, focused on immune-mediated arthritis and autoimmune-related acute and chronic disorders in adults and children. As noted in the introduction to this plan, many of these diseases disproportionately affect women and groups historically underrepresented in biomedical research. While the underlying causes for these differences are largely unknown, progress is occurring in understanding them and translating that knowledge into effective treatments.

The results of NIAMS-funded research have paved the way for biologic therapies for systemic rheumatic and autoimmune diseases. These therapies have improved outcomes and quality of life for many patients, highlighting the importance of fundamental research in improving health. Going forward, NIAMS will continue to build on this progress to further understanding of systemic rheumatic and autoimmune diseases and to develop even more effective and personalized treatment approaches.

In adults, systemic rheumatic and autoimmune diseases and disorders include, but are not limited to:

- rheumatoid arthritis;
- systemic lupus erythematosus (or lupus);
- crystalline-induced diseases (gout, calcium pyrophosphate dihydrate crystal deposition disease, hydroxyapatite crystal disease);
- spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis);
- reactive, enteropathic, and infectious arthritis;
- systemic scleroderma and related conditions such as interstitial lung disease and Raynaud’s phenomenon;
- vasculitides (giant cell arteritis, polymyalgia rheumatica, granulomatosis with polyangiitis);
- Sjögren's syndrome; and
- fibromyalgia syndrome.

Pediatric diseases include all forms of juvenile idiopathic arthritis (JIA), childhood-onset lupus, scleroderma-related diseases, pediatric fibromyalgia, and periodic fever syndromes and other autoinflammatory disorders. Several aspects of these diseases differ between adults and children (e.g., risk factors, pathogenesis, outcomes), and these factors require special attention when conducting research on pediatric conditions.

Genetics, functional genomics, and epigenetics

Rheumatologists have long recognized the higher incidence of many rheumatic diseases within families and certain ethnic populations, suggesting that genetics play a role in risk. Perseverance in gathering biospecimens and clinical histories from patients and their relatives—along with the explosion of knowledge and technological advances in genetics and genomics—have opened new research avenues.

Functional genomics, gene regulation, epigenetics, and gene-environment interactions

Genome-wide association studies (GWAS) and other genomic approaches, such as whole genome or exome sequencing, have identified a series of genes and gene polymorphisms, also referred to as genetic variants, that relate to disease risk and severity in different populations. Some of these polymorphisms point to common gene regulatory elements that may be shared in many autoimmune diseases. The discovery of genetic variants, most of which reside within non-protein-coding regions of the genome, has advanced understanding of disease mechanisms, facilitated identification of potential pathways to target for therapy, and improved the assessment of disease risk. Despite progress in understanding some of the genetic variants involved in autoimmune and systemic rheumatic diseases, and in genomics approaches that have identified tens of thousands of genetic variants, the functional significance of most variants remains largely unknown. Follow-up studies are needed to understand how they may interact with each other, regulate expression and activity of target genes, and contribute to changes in cell functions and cell biology in ways that may affect disease risk and pathology in disease target tissues.

Environmental factors (e.g., gut microbes, dietary components, chemicals, ultraviolet light, infectious agents) may interact with the host by influencing gene activities or turning on or off genes to affect an individual's risk for diseases such as lupus, rheumatoid arthritis, and scleroderma. Environmental factors influence disease risk by interacting with the genome to alter gene expression without changing the underlying DNA. Analyses of these epigenetic changes, as well as genetics and transcriptomic data, are expected to provide novel insights into the development, progression, and severity of rheumatic diseases.

Broad areas of potential research directions include:

- Developing machine learning methods that combine layers of 'omics data (e.g., genomics, proteomics, metabolomics) to generate new mechanistic hypotheses and inform discovery of novel drug targets;
- Applying novel approaches to study the function of genetic variants, including novel gene editing techniques (e.g., CRISPR/Cas9), to assess the functional effects and

therapeutic potential of candidate variants (enhancers, promoters, noncoding RNA) and epigenetic regulation in relevant cells, model systems (e.g., induced pluripotent stem cells), and in knockin or knockout (e.g., RNAi) in vitro and in animal models;
- Understanding epigenetic mechanisms that link genotype to phenotype in rheumatic diseases;
- Extending genetic and genomic studies to understudied ancestral populations (e.g., non-European) to better understand the biological basis underlying differences in disease susceptibility;
- Applying scalable, single-cell analysis approaches, such as parallel analyses of proteins and gene expression and the epigenetic landscape in the same sample, to enhance understanding of disease by analyzing large numbers of samples;
- Leveraging novel spatial multi-omics tools and approaches developed by the Human BioMolecular Atlas program to further map molecular and cellular interactions in healthy and disease tissues;
- Applying novel strategies to dissect the major histocompatibility complex loci associated with rheumatic diseases; and
- Studying gene-gene, gene-protein, and gene-environment interactions using novel or enhanced analytic approaches.

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 investigating the influence of genomic variations on drug responses, including drug efficacy and toxicity. The application of genomic approaches to well-characterized longitudinal clinical cohorts holds great promise for development of personalized medicine for systemic rheumatic and autoimmune diseases.

Broad areas of potential research directions include:

- Leveraging well-characterized patient cohorts and tissue repositories, along with novel and robust genetic and genomic approaches, to understand the underlying mechanistic differences in treatment responses and drug toxicities;
- Integrating genetic and genomic information to improve clinical trial design;
- Defining disease heterogeneity at the molecular level by applying genetic and functional genomic information, as well as other relevant factors, to foster refinement of phenotypes and subcategories of complex diseases;
- Translating genetic and genomic information into clinically actionable algorithms to aid in identifying individuals at high risk for disease and to improve clinical diagnosis, prognosis, treatment selection, compliance, and health-related quality of life;

- Developing high-throughput methods to screen existing or novel molecules and drugs for targeting genetic/genomics-associated pathways with rapid transition to proof-of-concept trials; and
- Exploring novel approaches in pharmacomicrobiomics (a subfield of genomics, microbiomics, and pharmacology) to understand the effects of the interaction between xenobiotics or foreign compounds and the gut microbiome on treatment responses and toxicities in systemic rheumatic and autoimmune diseases.

Mechanisms of disease

Innate and adaptive immunity

Increased knowledge of basic functioning of the immune system, and in particular, the fundamental biology of autoimmunity, has advanced our understanding of systemic rheumatic and autoimmune diseases. The two arms of the immune system—the innate and adaptive arms—coexist as protective and potentially injurious forces. Successful immune response depends on the body's ability to produce diverse receptors on the surface of immune cells. The innate immune system is the body's first line of defense and reacts quickly and broadly to environmental or pathogenic insults to the body. It consists of anatomical barriers, networks of soluble mediators, and effector cells. In contrast to the innate immune system, the adaptive immune system provides more specific, targeted, and sustained responses. Because of the enormous number of antigens that the body routinely encounters and their potential similarity to the body's own 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. 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 enhance development of antigen-specific and/or autoreactive, personalized, cell-specific therapies that leave protective, global immune function intact.

Broad areas of potential research directions include:

- Studying the role of innate immune system components—DAMPs, PAMPs, PRRs, inflammasomes, and associated signaling pathways—in 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;

- 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, natural killer cells, mast cells, basophils, eosinophils, fibroblast, and synoviocytes;
- Exploring the role of stem and progenitor cells in immune and autoimmune processes;
- Applying single-cell analyses to further define the role of cell subsets and functional plasticity in innate and adaptive immune responses and autoimmune rheumatic diseases (e.g., diversity and plasticity of the monocyte-macrophage lineage in promoting or resolving inflammation, role of T and B cell subsets);
- Understanding the contribution of dysregulated cellular processes (e.g., citrullination, programmed cell death, autophagy, unfolded protein response, mitochondrial dysfunction) and altered metabolism in development and progression of autoimmune disorders and autoinflammatory diseases;
- Clarifying the role of the major histocompatibility complex and antigen-presenting cells in autoimmunity;
- 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 diverse roles of B cells in autoimmune diseases, including autoantibody production; antigen presentation and co-stimulation during initiation of immune response; and the release of inflammatory and immunomodulatory cytokines;
- Elucidating mechanisms by which sex-specific factors, such as sex hormones, sex-specific gene products (e.g., X and Y chromosome products), and other factors (e.g., pregnancy) influence immune functions to understand why autoimmunity is much more common in women; and
- Understanding the cellular and molecular mechanisms linking cancer and autoimmune diseases, both in terms of autoimmunity increasing the risk of cancer and autoimmune adverse events stemming from checkpoint inhibitor therapies.

Inflammation

Chronic inflammation is a characteristic of many autoimmune and autoinflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory myopathies, and lupus. Inflammation likely causes or exacerbates joint swelling, acute and chronic pain, fatigue, sleep disorders, depression, and organ damage. Research advances detailing molecular and cellular contributors to inflammation have provided critical insights into potential causes and the development of therapeutics in many rheumatic diseases.

Broad areas of potential research directions include:

- 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);
- Conducting further research on the role of immune cell subsets (e.g., T cells, B cells, dendritic cells, innate lymphoid cells) in the inflammatory processes in rheumatic diseases (e.g., the role of regulatory T cells in ameliorating inflammation);
- 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 examining the roles of the adhesion molecules and chemo-attractants that mediate cell trafficking;
- Exploring the biology of neural regulation of immunity and inflammation and the therapeutic implications of those mechanistic insights for rheumatic and autoinflammatory diseases; 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.

Pain

Pain is one of the most important symptoms affecting quality of life for patients with rheumatic diseases and chronic pain syndromes. Research on the biological mechanisms of pain in rheumatic diseases may lead to new approaches to manage pain.

Broad areas of potential research directions include:

- Investigating interactions involving the plasticity of the peripheral and central nervous systems, and the plasticity of the inflammatory system, that may contribute collectively to the development and perpetuation of chronic pain through its centralization;
- Implementing and comparing validated, universal, and disease-specific pain measures (e.g., PROMIS pain interference, behavior, quality, and intensity in pediatric and adult patients);
- Gaining a better understanding of both peripheral and central mechanisms contributing to chronic musculoskeletal pain and the transition from acute to chronic pain;
- Understanding how chronic inflammation may affect the brain and development of complex pain syndromes;
- 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 that make an individual susceptible to chronic pain, cause the transition from acute to chronic pain, or influence long-term outcomes of pain that begins in childhood;
- 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 for both adult and pediatric populations;
- Exploring the use of appropriate animal models of chronic pain to better understand its pathophysiology and etiology and to develop behavioral measures;
- 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 to improve both pain and related comorbidities such as fatigue, depression, and sleep disturbance; and
- Leveraging imaging and other biomarkers to better understand the mechanisms of acute and chronic pain to facilitate future novel treatment approaches.

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, intestines, blood vessels, and brain. Although immune dysregulation plays a major role in these diseases, the structure and function of target organs such as the vasculature may contribute significantly to the development of tissue damage and fibrosis in 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:

- Applying single-cell analysis and spatial multi-omic approaches to study cells and molecules present in target tissues or organs (e.g., synovium in rheumatoid arthritis; kidneys in lupus; skin, lung, and other organs in scleroderma);
- Exploring interrelationships between immune response components (both innate and adaptive) and target tissues or organs in normal and pathological conditions;
- Characterizing and understanding how autoantibodies cause disease and tissue damage;
- Investigating the role of nonimmune mechanisms (e.g., hypoxia, metabolic changes) in tissue injury;

- Exploring the role and mechanism of fibrosis in rheumatic diseases and the development of rheumatic disease-associated comorbidities (e.g., interstitial lung diseases, pulmonary hypertension, renal manifestations);
- Investigating the role of altered cellular homeostasis (e.g., extracellular matrix components, gut microbiome) in the development of inflammatory and autoimmune diseases;
- Characterizing the role of genetic factors in influencing the presentation and severity of disease in target organs;
- 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, progression, and treatment of cardiovascular disease in arthritic and rheumatic diseases;
- Investigating the role of cellular senescence and aging in the development of end-organ tissue damage and resolution;
- Studying the effect of symptom- and disease-modification-based therapies on organ damage;
- Investigating the role of the synovial entheseal complex in spondyloarthropathies;
- Studying the mechanisms of non-erosive inflammatory arthritis and musculoskeletal complications;
- 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.

Preclinical and translational research

Unraveling the complexity of rheumatic diseases to advance the development of effective and targeted interventions requires an understanding of how disease initiation and progression are integrated. Much of this research is conducted in model systems that lead to further refinement of therapeutic approaches and design before human testing.

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

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 available 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 human cell-based systems may also serve as important experimental models for studying systemic rheumatic and autoimmune 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.

Broad areas of potential research directions include:

- Developing clinically relevant animal models for functional and mechanistic studies of pathogenic pathways identified by human genetic research;
- Developing animal models that recapitulate molecular abnormalities identified in people with autoimmune diseases to improve understanding of disease mechanisms;
- Developing and using humanized mouse models that more closely recapitulate the human immune system to identify mechanisms important for human disease and test therapeutics;
- Using gene-modulation techniques (e.g., CRISPR/Cas9 for genome editing) to conduct large screens for phenotypes relevant to systemic rheumatic and autoimmune diseases (see also *Genetics, Functional Genomics, and Epigenetics*, above, for more information);
- 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; and
- Leveraging novel tissue engineering approaches to develop new model systems and improve existing complex in vitro, ex vivo, and organ model systems (i.e., three-dimensional models) for studying systemic rheumatic and autoimmune diseases.

Therapy development

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

Progress in Accelerating New Therapies in Rheumatoid Arthritis and Lupus

To increase the number of new diagnostics and therapies and reduce the time and cost of developing them, NIAMS is participating in the Accelerating Medicines Partnership (AMP)[1], a collaboration among NIH, the Foundation for the NIH (FNIH), the U.S. Food and Drug Administration (FDA), biopharmaceutical companies, and nonprofit organizations. NIAMS, in partnership with the National Institute of Allergy and Infectious Diseases, contributes to the AMP in two disease areas: rheumatoid arthritis and lupus. The AMP in rheumatoid arthritis and lupus[2] research network focuses on immune and tissue resident cells from organs affected by the diseases, including cells from the joints of individuals with rheumatoid arthritis and from the kidneys and skin of people with lupus. The network is adapting cutting-edge technologies to allow those cells to be analyzed individually using high-throughput approaches. At the same time, the network has pioneered important innovations in the conduct of research, including new models for collaboration among dispersed research institutions, groundbreaking strategies to build capacity for the acquisition of synovial and kidney biopsies in the United States, and standardization of sample processing protocols across multiple research sites. In addition, the program is making its data available to the broader research community to foster additional research on autoimmune diseases and enhance the return on investment in the program.

During the first phase of the program, investigators compared cells taken from the tissues of rheumatoid arthritis or lupus patients to cells from unaffected individuals with the goal of identifying changes in cells and biological pathways that occur in disease, but not in health. Results from phase I studies of rheumatoid arthritis revealed that certain subpopulations of immune cells and fibroblasts are increased in individuals with rheumatoid arthritis compared to controls.[3] Phase I studies of lupus uncovered subsets of white blood cells that are active in the disease and identified specific proteins that could be explored as therapeutic targets.[4] Other lupus phase I studies revealed differences between keratinocytes and kidney tubular cells of individuals

with lupus nephritis versus healthy controls in the expression of genes that respond to type I interferon proteins.[5, 6]

In the second phase, the network is exploring differences at the molecular level among patients with the same disease to determine why disease course and response to therapy can vary so widely among patients with the same disease. Understanding this variation could pave the way for precision medicine—the ability to tailor treatments to individuals. Early indications from the lupus studies suggest that differences in so-called "interferon signatures" between individuals with lupus can help predict whether a particular patient is likely to respond to therapy.[6] Additional phase II studies are expected to provide further insights into differences that could be used to personalize therapy for rheumatoid arthritis and lupus.

For further information see:

[1] The Accelerating Medicines Partnership website.
[2] The NIAMS website for the AMP Rheumatoid Arthritis/ Systemic Lupus Erythematosus Program.
[3] Zhang F, et al. *Nat Immunol*. 2019. PMID 31061532.
[4]Arazi A, et al. *Nat Immunol*. 2019. PMID 31209404.
[5] Der E, et al. *JCI Insight*. 2017. PMID 28469080.
[6] Der E, et al. *Nat Immunol*. 2019. PMID 31110316.

Broad areas of potential research directions include:

- Building on the successful treatment of adult rheumatoid arthritis with disease-modifying anti-rheumatic drugs, particularly early interventions to prevent progression to severe disease and tissue damage, to advance the development of therapies for other arthritic and rheumatic diseases of children and adults (e.g., lupus, scleroderma, ankylosing spondylitis, other spondyloarthropathies);
- Creating therapeutic strategies to target immune dysregulation in rheumatic and autoinflammatory 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);
- Fostering pharmacogenetic and pharmacogenomics research to investigate the molecular basis of individual therapeutic response using robust genetic and genomic approaches;
- Exploring tissue-remodeling pathways involved in end-organ damage to better understand pathophysiology and etiology of rheumatic diseases and to identify new therapeutic approaches;
- Improving patient stratification to enhance translational research studies including studies of remission, disease prevention and progression, and treatment response; and

- Exploring gene- and cell-based therapies to treat or prevent disease and combinations of drugs/biologics in treating rheumatic and autoinflammatory diseases.

Biomarkers

The goal of biomarker research is to use modern approaches to discover, validate, and qualify biomarkers for use in disease diagnosis, prognosis, and evaluation of therapies. In general, molecular/cellular biomarkers are measured 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 peripheral blood and organ-specific biomarkers that correlate with activation of specific pathways in tissues and can be used to predict disease risk preclinically and/or to monitor onset and disease progression;
- Applying new technologies including metabolomics to identify novel specific predictive biomarkers;
- Developing innovative disease monitoring strategies such as in-home testing;
- Accelerating the transition of promising biomarkers from bench to clinic using state-of-the-art statistical, analytical, and computational methods;
- 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; and
- Developing validated and standardized outcome measures to enable better assessment of biomarkers and success of interventions across diverse populations.

Imaging

Imaging early or late changes in 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 been used to detect structural pathology in rheumatoid arthritis and ankylosing spondylitis.

Broad areas of potential research directions include:

- Optimizing detection and quantitative measurements of structural pathology and inflammatory activity with MRI, ultrasound, optical tomography, or positron emission

tomography (PET) for assessing, classifying, treating, and monitoring therapeutic responses in systemic rheumatic and autoimmune diseases;
- Developing ultrasound techniques (including 3D) to guide treatment decisions about inflammatory joint conditions;
- Investigating the use of noninvasive imaging technologies in functional studies of disease prognosis and progression including intravital microscopy and improved fluorophores to gain new insights into cellular interactions and potential mechanisms of disease;
- Using novel imaging technologies to enable analysis of soft tissues, including heart, blood vessels, kidney, and brain, to assess end-organ damage in rheumatic diseases; and
- Leveraging functional MRI and other evolving and emerging neuroimaging techniques to better understand and potentially treat disease-associated features such as pain, fatigue, or altered cognition.

Clinical research

The complexity of systemic rheumatic and autoimmune diseases, the diverse presentation and progression of many of these illnesses across patient populations, and the occurrence of multiple comorbid (co-occurring) rheumatic and other complex diseases in the same person, creates significant challenges in the diagnosis and management of these conditions. NIAMS supports clinical research to advance understanding of these diseases and to develop effective therapies to prevent or treat them.

Clinical studies and 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 assessment of health outcomes. In addition, widely available modern imaging technologies (such as ultrasound, optical tomography, and MRI) as well as sophisticated wearable devices require testing in clinical trials to evaluate their utility in patient care and management.

Broad areas of potential research directions include:

- 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;
- Determining whether drugs approved for specific 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;
- 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 for development of more efficient clinical trial designs (by predicting cohort size) and more informed clinical decision making (cost-effectiveness, potential toxicity versus prevention, quality-of-life impact over time);
- Performing studies to better understand treatment and management of rheumatic autoimmune disease-related adverse events occurring after treatments such as immunotherapy for cancer;
- Investigating specific treatments and use of imaging approaches (including 3D) for adult and pediatric rheumatic diseases;
- Conducting clinical trials in pediatric populations to determine safety, dosing, and efficacy of drugs approved for use in adults with the goal of improving therapeutic options for children;
- Conducting research to improve outcomes for common disorders, such as gout and calcium pyrophosphate dihydrate crystal deposition disease, that are expected to worsen due to several factors affecting the U.S. and global populations (e.g., aging, obesity);
- Studying the pharmacogenomics of responders and nonresponders to pharmacologic and biological interventions in rheumatic diseases to direct therapies to appropriate subsets of patients;
- Developing, validating, and disseminating clinical outcome measures for rheumatic autoimmune diseases in adults and children, including outcomes needed to advance personalized therapies and novel trial designs;
- Conducting clinical studies to determine benefits of treat-to-target-trials as compared to current strategies that focus on the level of disease activity or symptoms;
- 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 comorbidities (e.g., pain, fatigue, depression) to standard therapy for rheumatic diseases in individuals with comorbidities;
- Developing functional outcome measures, including pain-related PROs, and biomarkers for chronic pain that could be used to assess the 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 and statistical approaches for rare rheumatic diseases; and
- Expanding the involvement of clinical practice physicians and other health care providers in community settings in large-scale trials.

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 comorbidities. Health services delivery requirements 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.

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 comorbidities (e.g., cardiovascular disease);
- Studying the long-term outcomes of chronic, systemic rheumatic, autoimmune and autoinflammatory diseases that begin in childhood;
- 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;
- Conducting research on environmental exposures, including the microbiome, that may contribute to rheumatic diseases, including systems epidemiology research to investigate the exposome, and integrate it with genomic, proteomic, and other “omics” datasets;

- 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 comorbid 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 infants; and
- Applying computational tools and mobile health technologies to epidemiological studies of autoimmune diseases.

Behavioral and biopsychosocial research

There is a need to better understand social determinants of health (defined as the conditions in which people are born, grow, work, live, and age), and the wider set of forces and systems shaping the conditions of daily life, especially for health disparities. Behavioral and social science research is contributing important epidemiologic information and approaches to managing mental health and distressing symptoms of these disorders. Interdisciplinary investigations that integrate behavioral, social, and biomedical sciences will likely enhance treatment and management of patients with rheumatic diseases, reduce disability, and may shed light on complex mechanisms involved in disease processes.

Behavioral

Broad areas of potential research directions include:

- Exploring cognition and cognitive dysfunction in rheumatic diseases, including use of brain imaging and assessment of relationships among cognition, mood disturbance, and disease activity;
- Generating theoretical models for the potential influence of stress on disease course and presentation (e.g., symptom flares) to evaluate the influence of stress management techniques and interventions on illness and to elucidate potential mechanisms of stress-illness interactions;
- Applying new approaches to study fatigue (e.g., PROMIS measures) in rheumatic diseases, focusing on epidemiological issues, potential mechanisms, prevention, and treatment;
- Exploring multidisciplinary approaches to investigate sleep disturbances and their relationships to disease processes, symptoms, and disability in rheumatic diseases; and
- Using mobile health technologies (e.g., smart phones) and web-based technologies to facilitate research on the role of behavioral factors in rheumatic diseases, such as efficient

collection of patient-generated data between clinic/study visits (e.g., telehealth), implementation of digital interventions, and the use of wearables (e.g., smart watches) involving a broad range of ethnic and social groups.

Psychosocial

Broad areas of potential research directions include:

- Studying the interaction of biological influences with social and/or behavioral factors 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 that may be affected by behavior, gender, ethnicity, family environment, prior trauma, education, or a combination of these factors;
- Exploring behavioral factors that influence patient interactions with providers and how this experience affects treatment response and long-term outcomes;
- Understanding the impact of stress and adverse childhood experiences on disease activity, including flares and overall health, to inform strategies for disease management, treatment, and prevention;
- Examining psychosocial prevention and intervention modalities proven effective in other disorders (e.g., diabetes, AIDS) to promote healthy behaviors and management strategies for people/patients with rheumatic diseases; and
- Addressing cross-cultural validation of outcomes instruments and other issues in pediatric rheumatology, including pain, psychosocial adjustment, physical functioning, and transition from pediatric to adult care.

Novel therapies

Broad areas of potential research directions include:

- Investigating use of integrative, complementary, and behavioral interventions (e.g., biofeedback, relaxation, physical therapy, mind-body interactions, cognitive behavioral therapy, exercise, diet, dietary supplements) to manage pain and fatigue symptoms associated with rheumatic diseases;
- Integrating patient-reported outcomes and clinical measures to support personalized 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 on disease management and treatment response; and

- Investigating the role of nonpharmacological treatments and combined individual, group, and technology-based interventions and evidence-based community programs for self-management and improvement of health-related behaviors.

Advancing and Accelerating Skin Biology and Diseases Research

NIAMS Skin Biology and Diseases programs fund basic, translational, and clinical research in skin, including both common and rare skin diseases. These programs include investigations of the basic molecular, cellular, and developmental biology of skin, as well as studies of skin as an immune, sensory, endocrine, and metabolic organ. Research on wound healing, autoimmunity, inflammation, heritable diseases, and birth defects is also included, with a focus on translating 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. Skin is an integral part of the human body, and skin function and skin diseases are influenced by 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.

Transdisciplinary 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 affecting skin as a whole or in specific regions of the body, as well as skin appendages such as hair and nails.

Skin molecular and cell biology

Understanding skin biology at the cellular and molecular levels is the foundation for elucidating normal and disease processes at the tissue level. These types of studies are intimately connected to the state-of-the-art technology and methodology used to understand DNA structure, chromatin organization, gene regulation, inter- and intracellular communication, and cellular control mechanisms and behavior in living tissues.

Broad areas of potential research directions include:

- Investigating chromatin structure and epigenetic mechanisms (e.g., noncoding RNA);
- Studying the 3D genome;
- Using 3D genomic data and other epigenetic data to determine how genetic variants in noncoding regions of the genome contribute to skin diseases;

- Studying transcriptional, co-transcriptional, and post-transcriptional regulatory mechanisms;
- Researching skin-specific cell biological mechanisms, for example, proliferation/differentiation, movement, sensing, intracellular transportation, secretion, signal networks, and intercellular communication;
- Identifying and characterizing novel populations of cells (single or small number) in human skin to improve understanding of cellular composition and heterogeneity;
- Investigating interactions between the skin and other organ systems, as well as systemic effects of perturbations in skin homeostasis; and
- Capitalizing on the accessibility of skin to pursue unique opportunities to develop real-time, in vivo, noninvasive methods for observation and intervention.

Stem cells

Skin structure and function are 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). 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;
- Identifying 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 interlineage conversion via dedifferentiation;
- Mapping cellular lineages in skin and determining how different cell types/subtypes interact with each other and identifying the importance of these interactions in 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.

Developmental biology

Skin is an organ containing multiple tissue types and appendages. How this complex structure arises from a simple epithelial layer during embryonic development has fascinated researchers for more than a century. Understanding skin developmental biology has contributed to recent advances in promoting skin regeneration and wound healing and in combating diseases.

Broad areas of potential research directions include:

- Understanding the developmental mechanisms of vertebrate skin;
- Defining specific genes, signals, and regulatory pathways in the development of skin and its appendages that shape skin as an organ; and
- Illuminating interactions among components of dermis and epidermis during development.

Skin as a barrier

The primary function of skin is to provide a physical barrier that is flexible, resilient to mechanical force, properly sealed, and capable of blocking ultraviolet radiation, 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 diseases.

Keratinocytes (epidermis)

Keratinocytes are the principal cells that form the body's outer physical barrier. They also contribute to other functions of skin (e.g., immune and sensory).

Broad areas of potential research directions include:

- Delineating the developmental pathways of keratinocytes to improve understanding of skin diseases, identify potential therapeutic targets, and enable researchers to convert iPS cells into differentiated keratinocytes;
- Investigating the structures and mechanisms that maintain structural integrity of epidermis or, when defective, contribute to the underlying pathogenesis of pemphigus, pachyonychia congenita, forms of epidermolysis bullosa, and other diseases;
- Studying changes in the skin permeability barrier caused by circadian rhythms, aging, and disease;
- Identifying targets for therapies to restore normal barrier function in disease and conditions such as premature birth;
- Determining how the skin barrier affects topical therapy and transdermal delivery for topical and systemic agents; and
- Investigating the role of keratinocytes in skin immune and sensory functions.

Skin photobiology and melanocytes

Electromagnetic radiation, visible or invisible, has many effects on normal and pathological skin physiology. A primary shield of this radiation is created by melanocytes, cells that possess unique properties that protect vital stem cells and subcutaneous tissues through the production and transfer of melanin to keratinocytes. 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);
- Determining melanocyte stem cell and lineage development;
- Investigating melanocyte cell biology and population heterogeneity;
- Studying melanosomes and melanin synthesis and transfer pathways;
- Exploring the role of melanocytes in overall skin photobiology (e.g., their interactions with other cell types); and
- Identifying molecular and genetic differences between preneoplastic and senescent nevi.

Skin fibroblasts and extracellular matrix

Basement membrane and dermis provide much of the structural support and mechanical strength of the skin barrier. Scientists are just now appreciating the role of extracellular matrix (ECM) in regulating cytokine activity and cellular behavior. A major focus of research in this area is determining how fibrosis develops. Another important area is understanding inherited defects in ECM proteins, that is, heritable connective tissue disorders (see also *Genetics*, below, for more information).

Broad areas of potential research directions include:

- Investigating the biology of normal fibroblasts and their transition (e.g., transdifferentiation to myofibroblasts) during normal and diseased physiology;
- 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; see also *Skin as a Sensory and Endocrine Organ*);
- Uncovering interactions between epidermal and dermal components and the role of these interactions in the development of diseases;

- Studying mechanisms that control the normal assembly, interactions, and function of molecular components of the ECM;
- Studying regulatory function of the ECM and ECM-cell interaction; and
- Understanding mechanisms of ECM-related diseases.

Skin vasculature and adipose tissue

The cutaneous vascular plexus of the dermis/hypodermis is a dynamic, environmentally responsive network of blood vessels that provides nutrients, acts as a conduit for the immune system, and is involved in thermoregulation and wound healing. The skin is also home to an elaborate network of lymphatic vessels that parallels the major blood vascular plexuses and enables clearance of fluids, macromolecules, cells, and foreign material from the dermis.

Subcutaneous adipose tissue has been understudied, and recent advances suggest that in addition to thermo-insulation, its functions also include regulation of wound healing, fibrosis, hair cycling, and the innate immune response to bacterial infection.

Broad areas of potential research directions include:

- Expanding understanding of mechanisms controlling angiogenesis, lymphangiogenesis, and structure and function of blood/lymphatic vessels in normal skin development;
- Investigating and understanding the cellular/molecular biology and genetics of skin vasculature that contribute to cutaneous vascular malformations or affect angiogenesis in chronic wounds and in inflammatory and fibrotic diseases; and understanding the cause of skin vasculature birth defects (e.g., hemangioma and port wine stain) and developing effective therapies;
- Researching the role of adipose tissue in skin homeostasis and whole-body physiology; and
- Studying the role of adipocytes in skin repair, regeneration, and fibrotic diseases.

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. A large repertoire of cell types performs multiple functions during this process: covering the wound bed, fighting microbial infection, and rebuilding tissue architecture, an inherently multifaceted process.

Broad areas of potential research directions include:

- Studying the molecular basis of barrier leakages and their consequences;
- Assessing 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;
- Investigating 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, connective tissue, and mesenchymal, immune, and inflammatory cells;
- Researching the milieu of slow-healing and chronic wounds to identify factors that impair healing;
- Defining molecular and genetic mechanisms that contribute to aberrant/exuberant wound healing, fibrosis, or scar/keloid formation; 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.

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, neurons, hair follicles, 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.

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, dermal dendritic cells, macrophages, monocytes, innate lymphoid cells, and

others also screen the external microenvironment, epidermis, and/or dermis. Importantly, microbial commensals help the skin-based immune system mature and release factors such as AMPs that antagonize pathogen invaders. Skin is also innervated, and the functions of immunocytes, keratinocytes, and neurons are linked. 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 understanding 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 innate and adaptive immunocytes, as well as their receptors and soluble factors (using single-cell RNA sequencing, CyTOF, and other new technologies);
- Developing in vivo and in vitro 3D skin models, including skin on a chip, that include immune components, to define key regulatory signaling pathways activated in human keratinocytes and/or immunocytes;
- Discovering new mechanisms by which commensals, neurons, keratinocytes, and immunocytes interact and synergize;
- Defining bidirectional molecular signals that skin microbial communities use to communicate with each other and with the cutaneous immune system;
- Determining how changes in the skin barrier affect the ecology of the microbial communities on the skin's surface and their access to the dermal compartment;
- Identifying mechanisms by which resident microbiota of the gut, lung, oral cavity, and other mucosa affect skin's resident microbial communities;
- Defining the role of glycobiology in skin immune responses;
- 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, the endocrine system, and the nervous system communicate in healthy and diseased skin;
- Developing intravital imaging and nanotechnology to study skin structure, cell migration, cell interaction, and intracellular trafficking in live skin;
- Analyzing influences of subcutaneous adipocytes and corresponding lipid metabolism in the control of skin immune functions; and
- Defining the role of the skin immune system in the initiation, development, and surveillance of skin cancer.

Inflammatory and immune skin diseases

The easy accessibility of skin facilitates molecular and cellular analyses of lesions and enables a systems biology approach to studying inflammatory and autoimmune skin diseases. These types of studies identify functional signatures of these diseases, for example, differentially regulated genomics, epigenomics, transcriptomics, proteomics, and metabolomics, and changes in activated cellular subsets, antibody and receptor repertoires, signal transduction pathways, and the microbiome.

Genetic and epigenetic studies of skin immune diseases

Additional research is needed to improve understanding of cellular and molecular mechanisms that contribute to complex skin disease pathogenesis. Artificial intelligence and computational models that integrate information obtained from high-throughput proteomics, transcriptomics, genome-wide association studies (GWAS), deep genome-wide sequencing studies, the **Enc**yclopedia **o**f **D**NA **E**lements (ENCODE) project, 3D chromatin structure and epigenetic markers data, and functional genomic studies will reveal novel mechanism by which genomic and proteomic alterations result in clinical manifestations of skin immune diseases.

Broad areas of potential research directions include:

- Using genetic and functional genomics approaches to investigate pathogenic mechanisms and skin disease progression; and
- Studying roles of gene-environment interactions, epigenetics, noncoding regulatory DNA, chromatin interactions, and other modifiers of gene expression (e.g., microRNAs, lncRNAs) in disease pathogenesis.

Pathogenesis studies

More research is needed to discover innate and/or adaptive cellular and molecular mechanisms that trigger and control pediatric and adult inflammatory and autoimmune skin conditions such as hidradenitis suppurativa, Steven-Johnson-TEN, pemphigus, pemphigoid, psoriasis, atopic dermatitis, ichthyosis vulgaris, alopecia areata, cicatricial alopecia, vitiligo, acne, rosacea, immune-mediated itch, and others, and to understand comorbidities associated with them. Activities described in the box “Understanding Co-occurring Conditions in Psoriasis” are examples of research to address comorbid conditions associated with psoriasis.

Understanding Co-occurring Conditions in Psoriasis

Certain chronic diseases seem to occur together. For example, psoriasis is associated with an increased risk of developing conditions such as cardiovascular disease, diabetes, depression, and psoriatic arthritis. Managing the care of patients with multiple simultaneous health issues, often referred to as comorbidities, is challenging. In addition, patients with multiple chronic conditions may have worse health outcomes and quality of life than other patients. Recognizing the importance of addressing co-occurring conditions, NIAMS supports research to understand why such conditions develop, identify patients at highest risk for them, and determine how best to treat their conditions.

As part of its investment in psoriasis research, NIAMS supports a varied portfolio of efforts related to co-occurring conditions. A 2017 NIAMS roundtable brought together researchers in dermatology and rheumatology to discuss research needs in psoriatic arthritis, a form of joint inflammation that can occur in people with psoriasis.[1] A NIAMS-funded translational research center is using cutting-edge technologies and clinical and laboratory data from patients to help predict which patients are most likely to develop comorbidities and to identify drugs that could be repurposed to treat them.[2]

Several NIAMS-funded studies have provided information that could improve treatment and management of psoriasis comorbidities. One such project, which examined the risk of type 2 diabetes in people with psoriasis, suggests a link between psoriasis severity and the development of diabetes.[3] The results underscore the importance of diabetes prevention in psoriasis, especially for those with severe disease. Another study showed that individuals with psoriasis, particularly those prescribed a systemic therapy, that is, a drug that spreads throughout the body, are at increased risk for developing liver disease. This suggests that patients on systemic therapy should minimize exposures, for example, to certain medications, that may damage the liver.[4] Other work supported by NIAMS tested whether the anti-inflammatory drug adalimumab mitigates the increased cardiovascular risk seen in patients with severe psoriasis.[5] Although the drug was not effective at reducing cardiovascular risk factors, the results provide important new information for clinicians as they decide the best course of treatment for their patients.

For further information see:

[1] Summary of the 2017 Roundtable.
[2] The Center of Research Translation Project Information.
[3] Wan MT, et al. *J Am Dermatol*. 2017. PMID: 29128465.
[4] Ogdie A, et al. *J Invest Dermatol*. 2018. PMID: 29104161.
[5] Metha NN, et al. *Circ Cardiovasc Imaging*. 2018. PMID: 29776990.

Broad areas of potential research directions include:

- Using artificial intelligence and machine learning to define personalized medicine profiles through integration of electronic medical records and patients' cellular and molecular signatures;
- Including diverse populations in the creation of artificial intelligence systems to improve understanding of disease manifestations in different skin types;
- Investigating unique or shared cellular and molecular mechanisms involved in the onset, development, and progression of immune-mediated skin diseases;
- Investigating CD-1-based glycolipid skin immune responses and their role in inflammatory skin diseases;
- Using single-cell RNA sequencing to study cells isolated from skin biopsies of human inflammatory skin disorders;
- Exploring the mechanisms by which cytokines, chemokines, or autoantibodies cause symptoms in skin diseases to inform development of drug therapies;
- Studying the role of the skin and gut microbiomes as potential triggers and regulators for autoimmune and inflammatory diseases of skin;
- Investigating innate and adaptive signaling pathways that contribute to skin disease symptoms and comorbidities (co-occurring conditions) such as cardiovascular disease, metabolic syndrome, and diabetes;
- Using epidemiology "big data" and analytical methods to link skin diseases with systemic comorbid (co-occurring) conditions;
- Characterizing altered lipid metabolomics and glycolysis pathways leading to inflammatory and autoimmune skin diseases; and
- Understanding the role of T cells, for example, the role of resident memory T cells in skin diseases including mechanisms of treatment failure and longevity of treatment effects.

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. 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 and remain relevant to this Strategic Plan.

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 normal and pathological conditions;
- Examining mechanisms of touch and temperature sensation;
- Investigating interactions among skin sensations, that is, 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; and
- Understanding skin's endocrine function.

Skin appendages

Skin appendages, for example, 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.

Genetics

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, polygenic, or mosaic, including sequence variations in protein-coding DNA and in noncoding regulatory regions that operate through genetic and epigenetic mechanisms. A better understanding of these genetic and epigenetic factors, as well as how the variants and mutations

contribute to disease phenotype, is essential to develop effective therapies. A large repertoire of therapeutic modalities is employed to combat heritable skin diseases.

Broad areas of potential research directions include:

- Using high-throughput genomic and other technologies (e.g., GWAS, whole and exome sequencing) to discover new genetic underpinnings of skin diseases;
- Determining how genetic variants and mutations lead to disease phenotype;
- Defining modifier genes and the effect of genetic background on phenotype heterogeneity, disease risk, and severity;
- Identifying 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;
- Applying high-throughput genomic and epigenomic technologies, combined with computational methodologies, to elucidate regulatory networks involved in normal skin biology and in disease states;
- Deploying deep genomic sequencing technologies to identify postzygotic somatic mutations that lead to pathological changes;
- Applying single-cell genomic and epigenomic analyses to better understand cell heterogeneity in normal and diseased skin and to trace cell lineages during skin development and homeostasis; and
- Developing technologies that allow single-cell analyses to be performed on cells isolated from human skin biopsies.

Regenerative medicine

Regeneration mimics the embryonic process that shapes original tissue; therefore, it heals injury without the scarring and functional deficits associated with repair, which relies on the use of substitute, or "makeshift," material to close a wound rapidly. Because only limited tissue regeneration occurs in humans, treatment of large-area acute skin wounds, such as extensive burns and trauma, involves both regeneration and repair and a key challenge is how to restore tissue function after a wound is closed. Regenerative medicine in skin involves research on developmental processes, tissue neogenesis, stem cells, the skin microenvironment, and engineering approaches to create temporary tissue substitutes or modify wounds for improved healing and functional restoration.

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,* above).

Broad areas of potential research directions include:

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

Tissue neogenesis

Tissue neogenesis is the process of regeneration of lost or damaged tissues or organs in response to injury and contrasts with wound healing, which involves closing the injury site and scar formation. While non-mammalian vertebrates and some mammals can repair skin without scars, human adult skin has very limited regenerative capacity for scar-free repair. The complete regeneration of injured or diseased human skin remains the ultimate goal and a major challenge of regenerative medicine.

Broad areas of potential research directions include:

- Understanding skin's regenerative potential;
- Defining conditions that induce or hinder adult neogenesis;
- Discovering mammalian model systems that can fully regenerate skin and appendages, (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 promote exogenous cellular engraftment and investigating approaches to maintain transplanted cells' unique properties in vivo.

Engineered skin tissues

3D skin cultures mimic in vivo human skin better than monolayer cultures and provide the opportunity for the creation of patient-specific models of disease. These models can be used to

study disease pathogenesis and genetics, and to test new therapies. Engineered skin can also be used directly as a therapy.

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 3D 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;
- Investigating use of natural and artificial ECM components as biomaterials that provide appropriate structural and mechanical properties for generating functional skin; and
- Developing wound coverings for drug/growth factor delivery to promote healing and regeneration.

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.

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 humans. 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. Some complex diseases can be modeled with transgenic mammals, and some polygenic diseases (e.g., alopecia areata) have emerged spontaneously in mice and in other large animals.

Broad areas of potential research directions include:

- Developing animal models, using state-of-art technology (e.g., CRISPR/Cas, TALENs) and another approaches (e.g., optogenetics), to study the role of specific genes and regulatory pathways in the development of skin and its appendages, as well as in skin homeostasis, regeneration, skin microbiota, and heritable skin diseases and to test new therapeutic agents;

- Generating and validating animal models that mimic human skin diseases, including grafting of human skin and patient-derived or genetically engineered skin equivalents onto mouse skin, to examine molecular and cellular processes in a controlled experimental environment;
- Exploring naturally occurring mammalian models for skin biology, regeneration, and diseases (e.g., African spiny mouse or existing inbred mutant mouse strains);
- Exploring use of simpler organisms (e.g., zebrafish, flies) for modeling skin diseases and mutations and for high-throughput genetic screening;
- 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; and
- Developing specific animal models in conjunction with emerging observation technology (e.g., intravital imaging) to enhance the ability to detect, trace, and noninvasively identify cellular activity in vivo.

In vitro cell-based models

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

Broad areas of potential research directions include:

- Developing 3D tissue models of normal human skin and diseases;
- Using patient-derived iPS cells and other 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;
- Developing efficient, highly reproducible, and scalable protocols to produce differentiated skin cell types from iPS cells and methods to validate the identity of the resulting cells;
- 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.

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 biology 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 processes;
- Developing disease models (such as virtual patients) to inform clinical trial design and clinical practice; and
- Developing, with artificial intelligence concepts, methods for analyzing and understanding large data sets.

Therapy development

Knowledge of pathogenic pathways and basic skin biology facilitates development of small-molecule and biologic therapies (e.g., antibodies) that target specific components of these pathways. Such approaches enable 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, and that discussion remains relevant to this Strategic Plan.

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 nonresponders to pharmacologic and biological interventions in skin diseases with the aim of directing therapies to appropriate subsets of patients; and
- Developing interventions that reverse, not merely delay, adverse changes that occur in aging skin.

Gene and cell-based therapy

Correcting defective genes may be possible to treat monogenic skin diseases such as epidermolysis bullosa (EB) simplex. 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.

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, for example, 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, iPS, and embryonic stem cells to generate artificial bioengineered skin replacements for acute and chronic wounds and to repair or regenerate other tissues.

Cutaneous and transcutaneous drug delivery

The skin barrier makes targeted delivery of small molecules and biological drugs to the epidermis and dermis challenging. Conversely, the permeability of this barrier also presents an opportunity to consider transdermal delivery strategies to treat systemic diseases.
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.

Physical therapies

Several types of physical therapies are used in dermatology practice. Examples include phototherapy (e.g., ultraviolet light irradiation) and chemically modified water baths.

Broad areas of potential research directions include:

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

Clinical trials and outcomes measures

Clinical trials based on solid preclinical studies are essential for improving the public health. Combination therapies, evidence-based comparisons of treatments, and cost-effectiveness are critical topics for future research.

Broad areas of potential research directions include:

- Identifying clinical biomarkers that predict disease progression and treatment outcomes reliably and can be used as surrogate endpoints in clinical trials;
- Developing and validating new outcomes instruments that better measure disease severity and assess disease impact on quality of life for people and their families than current instruments;
- Developing methods to collect patient-reported outcomes and incorporate them in clinical studies/trials;
- Exploring alternative clinical trials designs 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 goal of improving therapeutic options for children;
- Establishing novel disease outcome measures and defining early signatures of disease onset and progression; and
- Exploring safety and efficacy of peptides and non-coding RNA-based therapy.

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 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 and burden on specific populations (e.g., underserved);
- Facilitating observational and epidemiological studies of skin disease comorbidities (co-occurring conditions) and gene-environment interactions that may trigger or exacerbate skin diseases;
- Investigating skin disease comorbidities (co-occurring conditions) as they relate to health disparities and therapeutic interventions;
- Examining the cost-effectiveness and comparative effectiveness of therapies and combination-therapy approaches for skin disease treatment and developing the infrastructure needed to conduct these studies;
- Investigating racial and ethnic differences in skin diseases to improve understanding of the effect of skin type on diagnosis, treatment response, and other issues;
- Researching effects of patient-health care system interactions on disease outcomes, considering in particular minority and underserved populations; and
- Developing new methods to collect data (e.g., mobile device, Internet, remote sensing) for epidemiological studies.

Prevention studies

Prevention studies are critical to promote health through the identification of risk factors for skin diseases, disorders, or injuries. They are also important for detecting and preventing progression of asymptomatic or early-stage skin conditions.

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.

Behavioral and biopsychosocial research

Changing lifestyle and habits can prevent many skin diseases, which provides opportunities for behavioral intervention. Furthermore, people with skin diseases are frequently affected by psychosocial problems due to social stigma. These factors highlight the role of behavioral and biopsychosocial research in combating skin diseases.

Broad areas of potential research directions include:

- Using social, commercial, economic, gender, ethnic, and cognitive data to understand correlations between behavior and skin diseases;
- Exploring interventions, including behavioral modification and protective strategies, to prevent skin exposure to environmental harm that causes disease and accelerates skin aging;
- Studying mechanisms by which stress affects skin disease progression and wound healing, and how stress management affects disease outcomes and treatment response; and
- Investigating management of chronic symptoms, such as itching and pain, as well as ways to minimize effects of these symptoms on stress level, sleep, and overall quality of life.

Advancing and Accelerating Bone Biology and Diseases Research

The 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 associated morbidity and reduced quality of life. In the United States today, more than 53 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 after menopause—prevention, diagnosis, and treatment of osteoporosis will continue to have major public health implications as the U.S. population ages. *Healthy People 2030*, the Nation's public health agenda, will seek to improve osteoporosis-related outcomes.

NIAMS supports studies on the control of bone remodeling (bone formation, bone resorption) and mineralization, as well as the effects of hormones, growth factors, and cytokines on bone cells. The Institute has overseen several large epidemiologic cohorts to characterize the natural history of osteoporosis and identify genetic and environmental risk factors that contribute to fracture. NIAMS also supports clinical trials to test the effectiveness of interventions to prevent fractures associated with osteoporosis and other metabolic bone diseases. In addition, the NIAMS Bone Biology and Diseases programs support research on the causes, pathophysiology, and treatment of less common bone diseases, such as osteogenesis imperfecta and Paget's disease of bone, as well as a wide range of developmental disorders of the skeleton, many of which are genetic.

Bone biology, physiology, and development

Molecular and cellular mechanisms in bone

Bone cells perform key processes in bone remodeling: formation of new bone by osteoblasts and resorption or breakdown of old or damaged bone by osteoclasts. In a healthy adult skeleton, these processes are balanced through 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. In addition, cells lining the bone surface play an important role in normal and pathologic remodeling. Disproportionate resorption compared to formation results in bone loss and can increase risk of fracture. Understanding mechanisms that regulate osteoblasts, osteoclasts, and osteocytes and influence bone resorption or bone formation may yield new therapeutic targets. Manipulating such processes could also be essential for tissue-engineering technologies using bone-forming cells.

Broad areas of potential research directions include:

Bone anabolic mechanisms: osteoblasts and osteocytes

- Characterizing biochemical pathways that control proliferation of osteoprogenitor cells;
- Defining populations of progenitor cells and early and intermediate cell types during differentiation to mature bone-forming osteoblasts and osteocytes, as well as mechanisms of transdifferentiation in tissue development and repair;
- Identifying factors that control progression through cellular lineages; and
- Elucidating mechanisms that control osteoblast activity and determine the cell's functional lifetime.

Bone resorption mechanisms: osteoclasts

- 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
- Identifying biochemical pathways that control osteoclast activity and the functional lifetime of cells.

Bone homeostasis: osteocyte function and action

- Defining mechanisms that control osteocyte differentiation, including formation of osteocyte dendritic processes and the lacunar-canalicular system; and
- Identifying factors that modulate osteocyte activity in normal and pathophysiological conditions, including understanding the effects of diseases and their therapies on bone homeostasis.

Mineralization of 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;
- Determining the effects of various degrees of mineralization on bone's structural, functional, and mechanical properties; and
- Identifying the causes of pathological calcification of soft tissues and exploring measures to prevent or reverse inappropriate mineralization.

Cell-matrix interactions in bone

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

Cross-talk between 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);
- Characterizing sites where molecules with effects on other bone cells are produced;
- Investigating effects of signaling molecules originating in other bone cell types on target cells; and
- Defining the mechanisms coupling bone resorption with bone formation during the bone remodeling process.

Fracture repair

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

Bone response 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 by specific mechanical stimuli under different loading conditions.

Integrative physiology

Researchers have made considerable progress in understanding interactions between bone physiology and the broad network of biologic processes involving various organs and tissues. For example, muscle function and muscle mass influence fracture risk and energy metabolism affects muscle tissue and bone cells. Scientists are now poised to make further discoveries to help explain the connection between the skeleton and other mesenchymal tissues (e.g., fat, muscle, cartilage, tendon, ligament), physiologic systems (e.g., nervous, vascular, immune, digestive), tissue-specific microbiome, and energy metabolism. Bone likely functions as a target and/or regulator as it interacts with various systems during development, aging, and disease. Many drugs for conditions putatively unrelated to bone may have unanticipated skeletal effects, and bone-building drugs may have unanticipated effects on other tissues. Bone researchers in collaboration with interdisciplinary scientists who specialize in other organ systems and metabolic pathways could begin to fully define these interactions. These teams should consider not only bone but also other organs and systems that associate with bone as an integrative unit. They should also seek to understand how inputs from multiple systems received by the bone affect the body.

Broad areas of potential research directions include:

Bone physiology and energy metabolism

- Characterizing factors that determine whether mesenchymal progenitor cells differentiate into osteoblasts or adipocytes;
- Determining how body mass and composition influence bone homeostasis and strength, including the relationship between bone physiology and regulation of distinct fat depots (e.g., subcutaneous, visceral, marrow fat); and
- Elucidating the relationships among bone physiology, obesity, and energy/glucose metabolism.

Bone and the nervous system

- Determining the mechanisms by which the central and peripheral nervous systems influence bone physiology, including the influence of circadian rhythms on the skeletal system; and
- Defining the roles of neurotransmitters and neuropeptides in bone.

Bone and the hematopoietic and immune systems

- Clarifying the importance of interactions between bone cells and cells of the hematopoietic system, and of the innate and adaptive immune systems in both bone health and disease, 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.

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 vascular calcification in cardiovascular disease.

Bone and cancer

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

Bone as a component of joints

- Characterizing the interface and crosstalk between bone and cartilage in articular joints, including signals originating in bone that may contribute to osteoarthritis;
- Determining distinct or overlapping roles of bone and connective tissue in conferring benefits of physical activity, including responses to mechanical stimuli and interaction with energy metabolism and mitochondrial function;

- Defining mechanisms that lead to pathological bone formation in joints, such as osteophytes (bone spurs) or spinal stenosis; and
- Describing the structure and function of bone, ligaments, and tendons, as well as the joint interphase formation and mechanisms leading to enthesopathy.

Bone and muscle

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

Skeletal development and homeostasis

Bone shaping and growth during infancy and childhood are important for adult skeletal health. 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 lead to more effective methods for enhancing repair and regeneration of bone damaged by disease or trauma. Bone cells arise from specialized progenitor or stem cells that can differentiate to produce several 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:

Early skeletal formation and growth

- Determining the mechanisms that establish bone location and shape during embryonic development; and
- Exploring environmental factors that affect bone during growth and development.

Disorders of skeletal development

- Defining causal factors underlying skeletal development disorders, such as the osteochondrodysplasias and other rare bone diseases, to understand the role of specific genetic mutations that contribute to skeletal disorders; and
- Investigating biological mechanisms that are associated with mutations linked to skeletal development disorders, including cellular and molecular consequences of these genetic changes on developmental processes.

Stem cells

- Mesenchymal/skeletal progenitor cells
  - Defining mesenchymal cell lineages to identify multipotent precursors 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;
  - Defining the contribution of different populations of stem cells to the development and formation of bone structure; and
  - Investigating effects of regulatory factors, such as growth factors and bone morphogenetic proteins, on proliferation and differentiation of progenitor cells.
- Embryonic and pluripotent stem cells
  - Examining osteogenic differentiation of animal and human embryonic stem cells, including responses to growth factors and other regulatory molecules; and
  - Exploring the potential of iPS cells for differentiation along the osteogenic pathway, including differences between induced and embryonically derived stem cells and the effects of different strategies for inducing pluripotency.

Genetics, genomics, and epigenetics 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 the contributions of numerous genes and post-transcriptional epigenetic modifications, technological advances have opened the door to an unprecedented understanding of individual risk for disease as well as 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.

Nonetheless, much of the heritability of skeletal traits, such as bone mass and fracture risk, remains to be identified. In addition, causal variants underlying skeletal disease, as well as the biochemical processes influenced by those variants, are still largely unknown. Filling in these gaps will require an integrated analytical approach, incorporating multiple data types (e.g., single-cell analysis, epigenomics, proteomics, transcriptomics, machine learning, computational modeling) and large sample sizes to reveal functional aspects of the genome in humans and in animal models.

Broad areas of potential research directions include:

Functional genomics and epigenomics of skeletal cells and tissues

- 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;
- Characterizing genetics and epigenetics of skeletal cells, including their roles in cell functions at the single-cell level;
- Identifying causal variants and molecular mechanisms that influence skeletal traits;
- Continuing to define genetic differences that underlie variation in bone formation, maintenance, and turnover;
- Integrating insights from animal models with data from human studies to determine functional significance of specific coding and noncoding gene regions; and
- Applying systems biology methodologies, big data approaches, computational modeling, and artificial intelligence to the study of skeletal biology, as well as making use of big data resources, such as ENCODE and GTEx.

Translating genomic insights into skeletal health

- Determining mechanisms of genotype-phenotype interactions and variations on bone health;
- Utilizing genetically modified skeletal systems and bone cells to develop therapeutics to address genetic defects;
- Exploring how environmental exposures and aging interact with genetics, leading to bone disease; and
- Identifying genetic and epigenetic markers that predict drug responses of bone tissues and cells.

Mechanisms of bone diseases: Preclinical and translational research

Pathobiological/pathophysiological mechanisms

Discovering the underlying pathobiological and pathophysiological basis of bone diseases will advance the field of bone biology. Interactions between laboratory and clinical researchers are essential for translating basic discoveries into new drugs, treatments, and diagnostics. These relationships also foster clinical observations that can prompt basic and translational research.

Broad areas of potential research directions include:

Mechanisms of bone loss, disease, and regeneration

- Characterizing molecular and cellular mechanisms contributing to bone loss during common physiological conditions such as sex-hormone deficiency, vitamin D insufficiency, chronic inflammation, and steroid drug treatment;
- Defining biological mechanisms underlying the pathology of rare bone diseases, such as osteogenesis imperfecta, fibrodysplasia ossificans progressiva, and Paget's disease of bone;
- Applying knowledge of potential therapeutic targets to develop and test new interventions for rare bone diseases;
- Identifying differences and parallels in injured bone and connective tissue healing, including the origins of progenitor cells contributing to tissue regeneration;
- Investigating mechanisms of increased bone loss or fracture risk due to diseases of other organs and systems, such as HIV infection or diabetes, or due to inactivity or unloading as a consequence of aging, dementia, or other diseases or conditions that cause a patient to be bedridden; and
- Investigating mechanisms of bone regeneration and repair, the cells and signaling involved, and other factors that determine the success or failure of the repair process.

Treatment-related mechanisms or processes

- Elucidating biological processes that contribute to bone loss surrounding orthopaedic implants and developing bone-preserving strategies for implant recipients; and
- Examining potential mechanisms of rare adverse effects associated with bisphosphonates and other osteoporosis drugs, such as atypical femoral fractures.

Model systems

- Developing preclinical animal models that more accurately represent initiation and progression of bone disease in humans, including response to therapies and potential adverse effects; and
- Developing new models, such as organoid systems, to improve understanding of the effects of variants associated with disease.

Therapeutic mechanisms

Translational research characterizing the cellular and molecular mechanisms of disease may lead to new biological insights that advance the diagnosis or prevention of bone disease and inform the development of novel therapeutic agents.

Broad areas of potential research directions include:

Underlying biological mechanisms

- Defining biological mechanisms of action for widely used medications, such as drugs prescribed to prevent or reverse bone loss, including adverse effects (e.g., atypical femoral fractures);
- Examining why some therapeutic agents become less effective with long-term use; and
- Translating knowledge about mechanobiology and bone response to loading into strategies for promoting bone health, fracture healing, and bone defect repair across the lifespan.

Drug discovery targets and their potential

- Identifying molecular targets for new drug treatments with greater efficacy and less adverse effects;
- Exploring multimodal therapeutic approaches to treat osteoporosis; and
- Determining bone effects of drugs prescribed for diseases of other tissues and systems, which may have an impact on bone quality or fracture risk.

Gene-based therapies

- Developing methods for recovery and re-introduction of cells in the marrow stromal/osteoblast lineage;
- Exploring the potential of embryonic and iPS cells as mediators of gene-based therapies for disease of bone;
- Discovering innovative ways to use genetic modification of cells to correct genetic defects in bone 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.

Imaging and biomarkers of bone quality and fracture risk

Noninvasive measures of bone quality and fracture risk

Measuring bone mineral density (BMD) is widely considered a good screening tool for osteoporosis, but is an imperfect test for assessing the strength and fracture resistance of bone. BMD does not account for specific contributions of bone geometry, microarchitecture, and material properties that influence the ultimate mechanical performance of bone. Dual energy X-ray absorptiometry (DXA), the standard clinical measurement of BMD, is widely available and economical. However, more sensitive and sophisticated methodologies have been developed and provide a more detailed picture of bone quality and strength, such as quantitative computed tomography (QCT) with finite element analysis, high-resolution peripheral QCT, and high-field magnetic resonance imaging (MRI). The application of these newer technologies has improved our understanding of bone structure and function, but has not yet provided an alternative method for assessment of osteoporosis. Further studies may lead to improved prediction of fracture risk and monitoring of treatment response.

Broad areas of potential research directions include:

In vivo methods

- Improving existing in vivo methods to assess bone loss, response to treatment, and its relationship with surrounding tissues, such as fat and muscle;
- Applying novel technologies and methodologies in large cohorts of normal, at-risk, and diseased individuals to examine the connections among bone, fat, and muscle tissue;
- Developing and validating noninvasive methods to assess bone quality, such as magnetic resonance, QCT, infrared imaging, and ultrasound;

- Developing algorithms to improve the clinical assessment of fracture risk and to provide early indications of treatment effectiveness; and
- Developing and adapting existing noninvasive tools to assess essential musculoskeletal functions, including biomechanical aspects of bone and muscle.

Integrating and improving imaging methods

- Developing new technologies for enhanced high-resolution imaging of bone ex vivo;
- Developing methods to integrate data from various in vivo and ex vivo imaging methods; and
- Building prediction models for disease risk from various imaging methods.

Therapeutic targets

Understanding how architectural, material, and biochemical factors contribute to bone strength may identify new treatment targets or novel markers of bone health.

Broad areas of potential research directions include:

Biological marker studies

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

Clinical research for rare bone diseases

Observational studies for rare bone diseases

In addition to basic and translational pathophysiological research, the NIAMS Bone Biology and Bone Diseases program supports clinical research to advance the diagnosis, management, and treatment of rare bone diseases. Knowledge of disease development and progression, diagnostic tools, and therapeutic options vary across the rare bone diseases. Rare bone diseases often manifest in organ systems other than the bone and musculoskeletal systems. Thus, multidisciplinary research efforts that incorporate integrative physiology approaches to study comorbid conditions are encouraged. Further, because of the limited number of patients affected by these diseases, innovative clinical study designs are necessary. To accelerate research,

patients and patient advocacy groups are important partners and should be engaged throughout the clinical research process.

Broad areas of potential research directions include:

Natural history studies

- Conducting natural history studies in rare bone diseases using common data elements whenever possible to document disease progression, the range of disease manifestations, and response to existing treatment and disease management, including those that address unmet clinical trial readiness needs and development of outcome measures; and
- Documenting how the diseases affect patients' function, such as loss of independence and pain, using methodologies such as patient-, parent-, or physician-reported outcome measures.

Phenotype-genotype and biological marker studies

- Studying phenotype-genotype interactions/relationships; and
- Validating clinical or biological markers for disease development, progression, and therapeutic outcomes, including occurrence of side effects, to support the clinical development of new therapeutics.

Therapeutic development and intervention studies

There is great need for discovery of therapeutic interventions for rare bone diseases.

Broad areas of potential research directions include:

Drug development, characterization, and validation

- Developing novel therapeutics for rare bone diseases with greater efficacy and fewer adverse effects;
- Adapting and repurposing therapies developed for other diseases to treat rare bone diseases; and
- Characterizing and validating new therapies to determine their efficacy and safety profiles, using innovative trial designs to address the issue of scarce and precious patient resources.

Responses to therapeutic intervention

- Optimizing existing therapies through investigating different dosing, timing, and delivery system (pharmacokinetics);
- Determining responses to therapeutic interventions at multiple specific drug concentrations (pharmacodynamics) and their underlying mechanisms of action; and
- Determining how specific drugs interact with particular genetic alleles (pharmacogenomics).

Nonpharmacologic interventions

- Developing nonpharmacologic interventions such as physical activity, dietary modifications, and behavioral or biopsychosocial approaches to improve function and alleviate pain; and
- Involving patients and patient advocacy groups in the process of therapeutic development to determine feasibility and acceptability of interventions.

Outcome measures

- Incorporating outcome measures that indicate therapeutic effects on bone as well as other musculoskeletal systems and organ systems, considering therapeutic effects on the extra musculoskeletal system as a whole;
- Developing and validating biomarkers to predict patients' responses to therapies, including efficacy outcomes and potential adverse effects; and
- Incorporating patient- and physician-reported outcome measures in clinical design.

Clinical research for osteoporosis

Observational studies for osteoporosis

Characterizing osteoporosis development through clinical research is necessary to decrease prevalence, alleviate suffering, and lessen economic costs. Utilizing individual and population-based data to determine disease effects will enable better prevention approaches, produce safer therapies, improve quality of life, facilitate earlier identification of those at high risk, and reduce disparities associated with osteoporosis. Both large cohort and personalized medicine studies can yield useful information to improve bone health, prevent and treat osteoporosis, and enhance the quality of life of the millions of Americans who develop this disease.

Broad areas of potential research directions include:

Natural history, cross-sectional, opportunistic studies

- Identifying critical time points throughout the lifespan that influence susceptibility to bone diseases;
- Determining the role of sex, gender, race, and ethnicity in bone diseases and conditions;
- Understanding the role of pain in chronic skeletal diseases/conditions and on key outcomes;
- Exploring environmental factors (e.g., lead) that may influence bone health and disease; and
- Elucidating factors that contribute to fragility fractures.

Outcome measure development

- Developing prediction models for bone health, bone disease, and response to treatment that incorporate risk versus benefit analysis and patient preferences; and
- Enhancing development and validation of outcome measures, including incorporation of predictive biomarkers for efficacy or adverse effects and patient preferences.

Intervention studies for osteoporosis

Intervention studies to prevent and treat disease are essential to bring basic knowledge and translational research into clinical guidelines and practice. 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, such as dietary and exercise interventions. Novel study designs are needed for both prevention and treatment of osteoporosis. In addition, engaging patients and participants is essential to developing effective osteoporosis prevention studies and health promotion programs.

To better characterize specific research needs related to osteoporosis interventions, NIAMS participated in an NIH Pathways to Prevention effort, described in the box below.

NIH Pathways to Prevention Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention

More than 10 million people in the United States have osteoporosis.[1] Lifestyle changes, including exercise and a healthy diet, may help reduce a person's risk of fracture. However, medications are often needed to prevent fractures if a person has osteoporosis and are essential if a person has experienced a previous fragility fracture. Effective FDA-approved medications can prevent debilitating and sometimes life-threatening fragility fractures. Reducing osteoporosis prevalence and hip fracture incidence are among the major objectives of *Healthy People 2020* and *2030*, the U.S. Department of Health and Human Services' national health promotion and disease prevention initiatives.

Rigorous clinical studies have demonstrated that 3 to 5 years of osteoporosis medication therapy prevents fractures. Clinical guidelines recommend bisphosphonates as a first line of treatment for most people who have osteoporosis, but treatment rates are low and medication adherence is poor. Reports of rare but serious adverse events and greater public concern about them have coincided with a marked decrease in the use of osteoporosis drugs and a leveling off in what had been a promising decline in the incidence of osteoporotic fractures.[2,3] Furthermore, as osteoporosis is considered a lifelong condition, the use of medications continues to be the cornerstone of therapy for osteoporosis. However, the benefits and risks of long-term osteoporosis drug therapies are not fully known.

In October 2018, NIAMS, the National Institute on Aging, and the NIH Office of Disease Prevention hosted a Pathways to Prevention Workshop on the Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention to identify research gaps and suggest focus areas that could move the field forward. As part of the workshop process, based on an Agency for Healthcare Research and Quality (AHRQ) systematic review of the scientific evidence,[4] speaker presentations, audience input, and public comments, an independent panel issued a report that lays the foundation for future research activities.[5] Strategies for disseminating and implementing these findings will be developed by federal agencies to improve public health in FY 2020 and beyond.

[1] Wright NC, et al. *J Bone Miner Res*. 2014. PMID: 24771492.
[2] Wysowski DK, et al. *Bone*. 2013. PMID: 24063946.
[3] Michael Lewiecki E, et al. *Osteoporos Int. 2017.* PMID: 29282482.
[4] Fink HA, et al. *Ann Intern Med.* 2019. PMID: 31009947.
[5] Siu A, et al. *Ann Intern Med.* 2019. PMID: 31009943.

Broad areas of potential research directions, many of which are consistent with the recommendations from the Pathways to Prevention workshop, include:

Prevention

- Developing new therapies to prevent fractures associated with osteoporosis and related conditions, including behavioral or biopsychosocial approaches, such as exercise, nutrition intervention, and biofeedback;
- Determining the impact of nutritional status (e.g., macronutrients and micronutrients such as vitamin D) on bone health and fracture risk;
- Developing and testing strategies to promote bone health and prevent osteoporosis by improving nutritional status on a population level;
- Exploring effects of environmental factors, such as smoking and environmental toxins, on skeletal health and development of osteoporosis; and
- Developing and validating improved outcome measures for osteoporosis prevention interventions.

Treatment

- Assessing combinations of existing 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 (e.g., direct delivery to the skeleton) and exploring approaches that reduce side effects from drugs;
- Comparing the effectiveness of different therapeutic approaches;
- Developing and validating novel outcome measures and surrogate markers that could be used to improve clinical trial efficiency;
- Developing new therapies to treat osteoporotic fractures and related conditions in research areas that might include:
    - Behavioral/biopsychosocial (e.g., exercise, rehabilitation);
    - Pharmacologic: antiresorptive, anabolic, combination/mixed therapies; and
    - Combinatorial approaches;
- Developing new therapies to implement following a primary fragility fracture to prevent future fractures, such as behavioral and biopsychosocial interventions, pharmacological treatments, or combinatorial approaches;
- Optimizing dosing and length of therapeutic interventions to maximize clinical bone outcomes;
- Identifying patient subpopulations that will benefit the most from therapies and improving the rate of drug initiation in those populations;

- Developing models assessing the balance between risk and benefit for both short- and long-term osteoporosis therapies; and
- Developing effective drug holiday strategies to maximize therapy benefit while minimizing adverse effects.

Personalized medicine in osteoporosis clinical studies

Characterizing disease mechanisms in clinical studies may enable researchers and health care providers to distinguish among disease subtypes that have similar endpoints (e.g., fracture). Further, improved understanding of individual genetic variation in osteoporosis is expected to lead to better prediction of drug response and account for heterogeneity in response to treatment. Existing databases can be retrospectively mined for information about variations in disease manifestation and treatment response.

Broad areas of potential research directions include:

Interaction of biologic and environmental factors

- Developing improved predictors of fracture risk that reflect the contribution of the individual's environment, lifestyle (physical activity and dietary intake), the microbiome, and personal medical history;
- 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.

Drug interactions with other factors

- Exploring interactions between bone-active drugs and medications prescribed for other co-occurring conditions.

Dissemination and implementation research toward osteoporosis prevention

NIAMS recognizes the importance of disseminating and implementing research findings; yet such findings may not be widely disseminated or implemented across clinical and community health care settings. Behavioral and social science approaches should be incorporated, where appropriate, to facilitate their adoption and implementation across diverse populations.

Broad areas of potential research directions include:

Dissemination, communication, and implementation at all levels

- Improving dissemination, communication, and implementation at the patient, physician, and health systems levels to improve diagnosis, prescription, uptake of, and adherence to prevention and treatment strategies for osteoporosis.

Social and behavioral determinants of health

- Determining patients' and health care professionals' beliefs and perceptions regarding fracture-associated morbidity and mortality, the benefits and risks of medication, and how they compare with the existing evidence;
- Identifying physician and patient barriers preventing the administration and use of pharmacologic therapies by patients at high risk of fracture;
- Elucidating strategies to increase primary care physicians' consideration of fracture risk and risk/benefit balance of fracture prevention strategies in their evaluation of complex patients with comorbid conditions; and
- Evaluating factors (e.g., legal/liability concerns) that influence primary care physicians' decisions to prescribe pharmacologic therapies.

Strategies to improve implementation

- Evaluating cost-effectiveness of various treatments compared with usual care;
- Exploring the impact of adherence and nonadherence on outcomes;
- Developing clinical decision-making tools that incorporate risk/benefit modeling to facilitate informed and shared decision making between clinicians and patients about osteoporotic therapies;
- Identifying strategies at the patient, physician, and health care systems levels (such as fracture liaison services) that can improve diagnosis and treatment of osteoporosis and increase adherence of drug therapies; and
- Tailoring delivery of care to improve health outcomes.

Health disparities in fragility fracture incidence, treatment, and outcomes

The emerging links between race, ethnicity, sex, age, disease status, and socioeconomic status and bone density, bone quality, and fracture risk suggest areas of genetic, biologic, and environmental diversity ripe for exploration. 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, or wrist. For example, African ancestry is generally seen as protective against

fracture, relative to European and Asian ancestry. However, bone health disparities are complex across and within groups. The changing demographics of the United States afford numerous opportunities for researchers to explore biologic and nonbiologic causes of disparities related to fragility fractures and to test strategies to ensure that all Americans benefit equally from efforts to monitor and improve bone health.

Broad areas of potential research directions include:

Biological influences on bone-related health disparities

- Investigating how mechanisms of action at the cellular and molecular levels (i.e., genetic studies) may vary among populations to affect bone health;
- Identifying differential responses to therapeutic interventions according to race, ethnicity, sex, and their underlying mechanisms; and
- Characterizing genetic and epigenetic factors that underlie ethnic, racial, and sex differences in bone mass, fracture risk, and fracture repair.

Other influences on bone-related health disparities

- Identifying barriers to participation of underrepresented populations in bone and other clinical research, and implementing strategies to reduce them;
- Developing and testing culturally relevant patient education materials to improve education and outreach in underrepresented populations and improve outcomes; and
- Evaluating effectiveness of established interventions in minority populations.

Advancing and Accelerating Muscle Biology and Diseases Research

The 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 to slow or prevent disease progression.

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 are presented in this NIAMS Strategic 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. That plan includes input from experts in the fields of muscular dystrophy pathophysiology, diagnosis, treatment, and patient and family care. NIAMS also partners with the National Institute of Neurological Disorders and Stroke (NINDS) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), with additional support from the National Heart, Lung, and Blood Institute (NHLBI) to fund the Paul D. Wellstone Muscular Dystrophy Research Centers program, an evaluation of which is described in the box below.

Evaluation of the Paul D. Wellstone Muscular Dystrophy Research Centers

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles. Many dystrophies also affect other organ systems, such as the heart, brain, blood vessels, and gastrointestinal tract. Some forms occur in infancy or childhood, while others typically appear later. NIH funds a broad portfolio of research into understanding and treating various forms of muscular dystrophy. One component of this research portfolio is the Paul D. Wellstone Muscular Dystrophy Research Centers program.

NIH established a muscular dystrophy Centers of Excellence program in 2003 in response to the Muscular Dystrophy Community Assistance, Research, and Education Amendments (MD-CARE) Act of 2001, and the centers became the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers in 2008. Although NIH has refined the program over the past 15 years, the neuromuscular disease research landscape has changed significantly since its inception. As the next award competition cycle approached, the principle of good stewardship

suggested that a comprehensive review of the Wellstone Centers program was timely and important. Therefore, the four NIH Institutes that support the Centers (NIAMS, NINDS, NICHD, and NHLBI) formed a Working Group of the NIAMS Advisory Council in FY 2018 to identify best practices for achieving the Wellstone Centers' goals of:

- supporting impactful basic, preclinical translational, and clinical research in the muscular dystrophies through synergistic projects;
- developing and broadly distributing resources that accelerate muscular dystrophy research;
- facilitating the training of the next generation of muscular dystrophy researchers and clinical scientists; and
- enabling connections with the patient community.

The Wellstone Centers Evaluation Working Group advised the NIAMS Council, and the report was shared with the NINDS, NICHD, and NHLBI Advisory Councils to inform their discussions about the Wellstone Centers program, especially the development of Wellstone Center Funding Opportunity Announcements. The report's executive summary, including the working group recommendations, is available online.

Muscle development and regeneration

Development

Understanding the process by which functional muscle fibers develop from their early, immature state may provide insights into disease mechanisms, regeneration strategies, and therapeutic targets.

Broad areas of potential research directions include:

- Determining lineage of cells that develop into muscle;
- 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.

Growth and maintenance

Studying the behavior of mature muscle under various environmental conditions (e.g., use and disuse, health and disease) is critical for developing strategies to repair or regenerate muscle.

Broad areas of potential research directions include:

- Characterizing cell types that contribute to muscle growth and maintenance, including the activation, migration, proliferation, and differentiation of muscle stem cells, such as satellite cells and other progenitors, during cell or tissue turnover and repair;
- Exploring satellite cell heterogeneity among individual fibers or muscles and among species;
- Determining when individual myonuclei become incorporated into muscle tissue during hypertrophy and their progenitor cell sources;
- Examining gene expression differences among muscle fibers or myonuclei and how they affect 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, and nutrition (including the microbiome);
- Exploring molecular and biochemical factors responsible for differences in muscle mass, susceptibility to atrophy, and response to exercise between men and women, people at different ages, or people from different racial backgrounds; and
- Studying the catabolic processes of autophagy and proteolysis as they relate to turnover of muscle fiber components.

Mechanisms of muscle function and dysfunction

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:

Excitation/contraction coupling

- Determining the structure and function of components of the sarcolemma and sarcoplasmic reticulum required for muscle cell excitation and intracellular calcium handling, including how membranes communicate;
- Defining calcium's role in contraction; and
- Exploring strategies to restore muscle function by optimizing intracellular, compartmental, and extracellular calcium and other ion concentrations and sequestration.

Structural biology and biophysics

- Elucidating the structure and function of macromolecular complexes essential for skeletal muscle function and maintenance, including dystrophin/glycoprotein complex, contractile apparatus, and ion channel complexes; and
- Characterizing protein complex assembly in more detail, including the roles of chaperones.

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;
- Characterizing in further detail how the contractile apparatus and links to the extra-cellular matrix are modulated during fiber repair and regeneration; and
- Investigating how muscle-strain injuries affect the components and organization of macromolecular complexes.

Mitochondrial biogenesis, turnover, and function

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

Integrated physiology and metabolism

The mechanisms by which muscle activity directly or indirectly contributes to the causes, prevention, and treatment of diseases and disorders affecting the musculoskeletal and other organ systems are a promising area of inquiry. For example, better understanding of the processes connecting muscle activity in the context of physical activity to disease prevention/amelioration may contribute to the use of exercise as a treatment for non-muscle related health conditions.

Broad areas of potential research directions include:

Muscle as an endocrine organ and metabolic tissue

- Defining metabolic and hormonal interactions between muscle and other tissues during normal, exercised, and diseased states;
- Examining muscle's role as a heat-producing organ in the regulation of core temperature;
- Exploring environmental effects and gene-environment interactions on muscle function;
- Identifying and characterizing factors released into circulation during skeletal muscle activity that affect other tissue and organ systems; and
- Investigating compounds that improve muscle's ability to metabolize energy sources.

Immune and inflammatory responses

- Characterizing positive and negative effects of inflammation on muscle regeneration after exercise, injury, or disease; and
- Determining mechanisms by which exercise alters immune responses.

Kinesiology

- Understanding muscle and muscle connective tissue interactions and the potential role of associated structural molecules;
- Improving understanding of how mechanical function of individual muscles determines energy use; and
- Determining how individual muscle recruitment affects gait and motion.

Pathophysiology

Just as research on normal muscle physiology is likely to uncover new 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:

Mechanisms of single gene muscle diseases

- Identifying gene mutations associated with muscle diseases with unknown causes;
- Characterizing genotype-to-phenotype correlations for muscle diseases;
- Understanding mechanisms of diseases caused by single-gene mutations, such as muscular dystrophies and channelopathies;
- Characterizing disease mechanisms to uncover potential therapeutic targets and better understand normal muscle biology;
- Elucidating how defects in gene expression (including epigenetic modifications) and post-transcriptional processing—including splicing, transcript modification, localization, and transcript stabilization or degradation—contribute to muscle disease;
- Understanding how defects in post-translational processing, such as glycosylation, contribute to muscle disease;
- Elucidating and examining factors, such as modifier gene variations and epigenetic changes, responsible for variation between and within muscle diseases, including disease onset, progression, and muscle groups affected; and
- Identifying compensatory gene products (e.g., utrophin for mutated dystrophin) and developing strategies to control their expression, accumulation, localization, and activity.

Muscle impairment associated with complex diseases and conditions

- Exploring mechanisms of muscle atrophy during prolonged bed rest or disuse often as a consequence of injury or critical illness such as cancer;
- Investigating skeletal muscle changes in cachexia in the context of diverse conditions including AIDS, cancer, chronic obstructive pulmonary disease, congestive heart failure, and end-stage renal disease;
- 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, to understand the genetic and environmental factors contributing to these conditions;
- Investigating mechanisms underlying muscle fatigue;
- 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 effective interventions.

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.

Interventions for muscle health

Development and use of model systems

Researchers can use model systems to define muscle development, function, and repair in healthy and disease states as well as to test approaches for preventing disease onset and progression. These models can be in vivo (animal), in vitro (cell culture or isolated tissue), or in silico (computer-based).

Broad areas of potential research directions include:

Animal models for understanding disease mechanisms and testing therapeutics

- Developing and characterizing mouse models of muscle injury, regeneration, and disease that more accurately reflect the genetics, pathophysiology, or clinical phenotypes observed in humans;
- Using non-mouse, genetically tractable developmental model systems, such as zebrafish, fly, and worm, to understand the genetics and cellular biology of normal and disease muscle;
- Establishing additional mid-size and large animal models to facilitate preclinical testing of candidate therapeutics in biological systems closer to the dimensions, biomechanical forces, and immune responses of humans; and

- Improving assays for characterizing animal models including enhanced in vivo imaging capabilities

Cell models

- Enhancing strategies for culturing, expanding, and differentiating various primary muscle and muscle stem cell models (e.g., satellite cells, iPS-derived myoblasts) for use in basic research studies and potential therapeutic applications;
- Creating human cell models (including 3D and tissue chip systems) that mimic in vivo conditions to study disease mechanisms and pathophysiology;
- Developing additional assays capable of reporting on muscle cell health and function including high-throughput, -omic, and live cell-imaging-based approaches; and
- Making cell models from individuals to enable personalized-medicine strategies and allow identification of compounds to which those individuals respond.

Computational models and artificial intelligence to study muscle function

- Developing computational models of muscle protein function to understand how genetic variants lead to muscle dysfunction and disease;
- Integrating models of inflammatory pathways in muscle for the identification of biomarkers and therapeutic targets for muscle disorders;
- Using human genomic approaches and computational modeling to develop a systems-level understanding of the role of muscle in health and disease;
- Improving models of muscle contraction and physiology from single muscles to multiple tissue types and their interactions (multi-scale models); and
- Modeling disease progression and treatment response to inform more effective and efficient clinical trial design.

Therapeutic interventions

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 nutritional, behavioral, and mechanical interventions. In addition to the development of interventions specific for muscle, drugs for other conditions are being tested for muscle applications (a process called drug repurposing). The FDA has approved two therapies for Duchenne muscular dystrophy in the last 5 years, and several additional candidate therapies for muscle diseases, such as gene therapy approaches for muscular dystrophies, are rapidly moving into human clinical trials.

Broad areas of potential research directions include:

Developing, repurposing, and enhancing interventions through:

Small molecule drugs

- Developing assays for high-throughput screening (including 'omics technologies) based on known mechanisms of muscle diseases to target pathophysiology (including resources such as the NIH Molecular Libraries and Imaging Program and NCATS Bridging Interventional Development Gaps Program);
- Using rational drug design or computational modeling to design novel small-molecule interventions based on molecular understanding of the pathogenesis or pathophysiology of muscle disorders; and
- Exploring public-private partnerships that increase the likelihood of successfully developing candidate therapeutics.

Biologics

- Developing biologics to treat muscle diseases based on activity of growth factors, extracellular matrix proteins, enzymes, and other gene products;
- Characterizing isoforms, subcomponents, metabolites, and mechanisms of action of potential therapeutic proteins and other biologics;
- Applying 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.

Gene transfer and genome editing therapies

- Characterizing properties of gene delivery vectors (viral and nonviral) to select those that facilitate efficient delivery of therapeutic genes to prescribed muscles of the body and minimize immune responses and delivery to unintended tissues;
- Continuing to develop approaches to control gene activity (e.g., regulatory cassettes) that maximize expression of therapeutic genes in specific target tissues;
- Developing a more thorough understanding of immune responses to gene transfer and genome editing therapies and designing interventions that avoid or minimize immune responses following initial and repeated delivery of therapeutic genes;

- Developing methods to assess and predict safety and efficacy of genome editing as it pertains to muscle disorders; and
- Advancing strategies for preparation of gene therapeutics that increase scale of production, reduce costs, and optimize purity and activity.

Cell therapies

- Characterizing abilities of growth factors, extracellular matrix molecules, scaffolds, or transcription factors to promote engraftment, survival, proliferation, and differentiation of cells that participate in muscle regeneration;
- Comparing migratory and regenerative potential of different cell types to establish characteristics 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.

Molecular therapies (including oligonucleotides)

- Continuing to develop oligonucleotides and other strategies to modulate the expression of gene products with the goal of compensating for mutations and restoring functions of proteins necessary for healthy muscle;
- Developing chemistries to synthesize and modify molecular therapies to improve their delivery and uptake by skeletal muscle, heart, and other affected tissues; and
- Characterizing gene products from exon-skipping strategies and evaluating the ability of those products to restore normal muscle function.

Nutritional and behavioral interventions, including exercise

- Leveraging knowledge about effects of mechanical stimuli on healthy and diseased muscle to develop biomechanical interventions;
- Studying mechanisms of exercise with the goal of developing physical activity-based interventions attractive to and convenient for people; and
- Investigating the response of muscle to feeding and nutrition, with and without exercise, including the timing of the intervention.

Devices

- Enhancing existing and developing novel devices for measuring muscle function, dysfunction, and health, and potential application of devices such as electrical stimulators in blunting atrophy or muscle degeneration; and
- Investigating devices (including but not limited to scaffolds) to improve therapy manufacturing or efficient delivery to muscle.

Combination therapies

- Investigating therapies that may have complementary or synergistic effects when used in combination, including determining optimal timing, dosing, and duration of treatment; and
- Exploring whether certain treatments may have antagonistic or detrimental effects when used in combination and ways to avoid or mitigate these consequences.

Muscle disease clinical research

Observational and natural history studies and clinical tool development

Observational cohort studies comprised of patients who have muscle diseases can provide essential information about disease symptoms, stages, and timing of disease progression, comorbid conditions, and outcomes that are important to patients. The development of biomarkers, clinical tools, and outcome measures could also inform clinical trials that are more efficient.

Broad areas of potential research directions include:

Diagnosis, natural history, and genetic modifiers

- Establishing rapid, precise, and cost-effective methods of diagnosing muscle diseases;

- Determining incidence and prevalence of muscle diseases in racial and ethnic groups;
- Conducting natural history studies to characterize patient phenotypic variations, disease course, and comorbid conditions, especially for diseases that have not been previously studied in this way;
- Identifying genetic modifiers that contribute to differences in muscle mass and strength, efficiency of muscle repair, susceptibility to atrophy or disease, and treatment response; and
- Applying known genetic modifiers in models and studies investigating genetic determinants of disease progression, and as a foundation for developing personalized medicines.

Biomarker discovery, characterization, development, validation, and use

- Continuing to discover, characterize, and validate diagnostic, monitoring, pharmacodynamic/response, predictive, prognostic, and safety biomarkers from an array of sources and approaches;
- Developing additional or enhanced imaging biomarkers through collaboration with imaging physicists, bioinformatics experts, or others, that are noninvasive and provide information about the size, shape, structure, composition, physical properties, and metabolic function of whole muscles or muscle groups;
- Integrating approaches such as elastography or electrical impedance myography into development of biomarkers that reflect physical properties of skeletal muscle; and
- Integrating biomarker data into databases and computational models 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.

Outcome measures (clinical and surrogate)

- Developing and validating outcome measures that span the entire course of disease to allow a wider range of patients to participate in clinical studies;
- Developing sensitive, accurate, and robust assays to measure proteins and other gene products from muscle biopsies and assess the restoration of these products;
- Refining measurement of muscle contraction, force production, musculoskeletal function, motor control, and other physiological functions (including physical activity) in a robust and unbiased way;
- Developing quantitative, noninvasive surrogate markers that can predict changes in physical function, disease severity, development of complications, or treatment response;

- Relating outcome measures and markers to meaningful changes in how an individual feels or functions as well as feasibility of including these measures and markers in clinical trials; and
- Improving and enhancing patient-reported outcome measures (PROs) for specific muscle diseases by incorporating patient input into PRO development and validating PROs developed for other diseases or conditions in people who have muscle diseases.

Care delivery and socioeconomic factors

- Evaluating patient transition to independence in adulthood, level of care, and accessibility of care, and using these data to develop testable hypotheses to reduce burden of muscle disease and improve quality of health services for patients of all ages; and
- Exploring how clinical care and management of patients with muscle diseases is influenced by socioeconomic factors, geographic locations, and other demographic variables.

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 first-in-human studies to demonstrate safety and proof of concept needed to launch efficacy trials;
- Conducting trials that test drugs, biologics, cell or gene therapies, molecular therapies, exercise regimens, or biomechanical or behavioral interventions that advance muscle-disease treatments;
- Evaluating potential additive or synergistic effects among interventions that have demonstrated efficacy;
- Applying data from natural history, biomarker, and genetic modifier studies to inform more efficient and effective trial designs and 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 nonambulatory patients can be included in the trial;

- Promoting interactions with patients, families, and caregivers to develop strategies to lessen the burden of study participation on patients and family members and focus on outcomes most important to patients;
- Standardizing outcome measures to allow for treatment comparisons addressed in different studies;
- Encouraging the participation of diverse populations in muscle research;
- Developing and testing specialized exercise “prescriptions” to maintain function, restore health, or improve quality of life;
- Pursuing pharmacogenomic testing strategies that will allow personalized care with optimal treatment regimens; and
- Conducting trials with behavioral interventions that address health services outcomes and daily living issues in people with muscle diseases.

Advancing and Accelerating Joint Biology, Diseases, and Orthopaedics Research

NIAMS Joint Biology, Diseases, and Orthopaedics programs fund a broad spectrum of basic, translational, and clinical research centered on the interplay among the body's muscles, bones, and connective tissues. These programs include research on the biology, structure, and function of joints and surrounding tissues and the application of this knowledge to a variety of diseases and conditions. Other programs fund tissue engineering and regenerative medicine to facilitate repair of damage caused by trauma to otherwise healthy tissue; molecular biology to understand the mechanisms of joint tissue formation and defects thereof; imaging to improve diagnosis and treatment of bone and joint disorders; and clinical research focused on treatment and prevention of acute and chronic bone and joint injuries and orthopaedic conditions, including musculoskeletal pain. Other sections of this plan address basic, translational, and clinical research interests related to bone, muscle, and rheumatic diseases.

Biology, structure, and function

Understanding the basic biology of joints and associated tissues is critical for the development of future basic and translational research studies. The complex interactions among the cells and tissues help define the physiological differences between healthy and diseased states.

Molecular and cellular biology of joint/orthopaedic 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 the microenvironment and the tissues from which those cells originate, will facilitate progress in this area. Since tissues do not exist in a vacuum, improved understanding of tissue crosstalk in development of and response to mechanical stress, as well as integrated physiology, provides a basis for translational and clinical studies.

Broad areas of potential research directions include:

Development, maintenance, and degeneration of tissues

- Characterizing molecules and signaling pathways that control cellular activities (e.g., stem cell renewal, pluripotency, and differentiation) essential for development and maintenance of relevant tissues (e.g., articular cartilage, growth plate, meniscus, ligament, tendon, and intervertebral disc), and for the development of tissue interfaces;
- Elucidating the effect of mechanical factors on cell signaling in development of joint tissues and in disease;
- Investigating the role of specific cell populations (e.g., tendon and meniscus progenitor cells, synoviocytes) and mechanisms of transdifferentiation in tissue development and repair;
- Examining influences of various connective tissue components during normal joint maintenance and repair or during joint deterioration caused by disease;
- Examining crosstalk and signaling among tissues involved in the formation and maintenance of joints (e.g., crosstalk between bone and connective tissue; immune response to mechanical stress or damage);
- Investigating the origins and mechanisms of joint degeneration; and
- Exploring synergies among therapeutic approaches that could yield improvements in the health and function of bone and connective tissue.

Articular cartilage and chondrocyte biology

- Characterizing interactions between cartilage matrix proteins;
- Studying mechanisms of cartilage matrix maintenance and attrition, including glycation and other post-translational protein modifications;
- Elucidating factors that contribute to chondrocyte cell death or chondrocyte proliferation under normal or pathologic conditions;
- Investigating structure and function of the bone-cartilage interface;
- Studying the role of mechanical stimuli on the formation, maintenance, and destruction of extracellular matrices; and
- Exploring robust, minimally invasive, and minimally destructive approaches to imaging and cell tracing in articular cartilage and in the developing growth plate.

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;
- Studying mechanisms of tendinopathy to identify biomarkers and therapeutic targets; and
- Developing cell-based therapies for tendons, ligaments, and menisci.

Research needs and opportunities related to innovative treatments for enthesis repair were discussed in greater detail at a 2017 NIAMS roundtable discussion.

Genomics and epigenomics

- Characterizing gene networks responsible for specification of articular cartilage and for growth plate development;
- Determining how mutations in individual cartilage matrix proteins affect chondrocyte behaviors and overall tissue structure and function;
- Exploring possible roles of epigenetic mechanisms in the differential onset and progression of joint and orthopaedic diseases;
- Studying mechanisms by which mutations, both coding and noncoding, and epigenetic differences contribute to joint and orthopaedic diseases;
- Determining how intracellular and extracellular noncoding RNAs influence cell behavior in healthy and diseased or injured tissues;
- Exploring genetic biomarkers or predictors of disease; and
- Investigating the effects of exosomal signaling and tissue crosstalk on gene expression, including resultant effects on the function of articular cartilage and related tissues.

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 posttraumatic 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:

Influence of biomechanics and injury

- Understanding the pathogenesis of post-traumatic OA (PTOA), including determining biomechanical factors (including gait) and biochemical pathways that influence initiation of joint changes associated with early OA, the progression of these changes to severe, late-stage OA, and joint deterioration/healing in response to acute injury;
- Developing and validating alternative models (such as in vitro human tissue models and/or preclinical large animals) that accurately recapitulate disease onset and progression and limit confounding effects;
- Investigating molecular signals that link mechanical loading with gene expression and the effects of that signaling;
- Understanding basic biomechanical effects and related biochemical changes from obesity that lead to or exacerbate the development of OA in children and adults; and
- Understanding the interaction among tissues surrounding joints, including cartilage, bone, muscle, tendon, and ligament.

Inflammation

- Further elucidating mechanisms in which nutrients and inflammatory signals are transported among the extracellular matrix, synovial compartment, and bone marrow;
- Defining the relationship between inflammatory signals and biological responses in joints, subchondral bone, and synovial tissue;
- Identifying signaling pathways triggered by joint inflammation, pathway origins, and their roles in joint degeneration;
- Distinguishing between inflammatory pathways and factors that are involved after acute injury and during chronic disease; 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 OA were discussed in greater detail at a prior NIAMS roundtable discussion.

Pain

- Studying the genetic, molecular, biochemical, and immunological pathways that give rise to painful osteoarthritic joints;
- Studying pain pathways activated during OA-induced mechanical stresses on joints; and
- Studying the bidirectional interaction between joint damage and pain mechanisms, including biopsychosocial mechanisms, and investigating discordance between structural damage and pain severity: structural abnormalities are ubiquitous as people age, but pain is not.

Genetic factors

- Defining the role of cellular aging and aging-associated epigenetic changes on OA onset and progression;
- Defining the role of epigenetic involvement of histone modification, DNA methylation, and tissue metabolism in pathogenesis of OA;
- Identifying and investigating genetically defined subsets of OA;
- Investigating early changes that occur in people with OA who advance to total joint replacement;
- Adapting existing cohorts to genetic studies;
- Determining contributions of gene-gene and gene-environment interactions to overall genetic influence on OA susceptibility; and
- Using genetically modified animals and genomic analysis tools to understand the genetic components (including noncoding variation) involved in joint degeneration and to develop approaches for treating and preventing disease.

Models for studying injuries and treatments

Although small animals, such as mice, have their utilities in biomedical research, their biological relevance for understanding adult human health is sometimes less robust. More research is needed to understand the parallels between small and large animal models. Some large animals (e.g., equines, certain breeds of canines) 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 on a single large-animal model to parallel research that has been conducted in mice?

Broad areas of potential research directions include:

- Developing well-characterized, age-appropriate animal models to study OA;
- Developing standardized protocols for behavioral and biomechanical assessment needed to accurately phenotype animal models;
- 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.

Regenerative medicine

Regenerative medicine is an area of science that seeks to develop new approaches for treating and even curing a variety of musculoskeletal injuries and diseases. It includes using stem cells and other technologies—such as engineered biomaterials and gene editing—to repair or replace damaged or aged cells, tissues, or organs, and aims to restore tissue/organ structure and function by tissue engineering and gene, cell, and pharmacological treatments. Multi- or interdisciplinary and collaborative research efforts involving both the life and physical sciences play key roles in moving this field forward.

Some of broad directions in regenerative medicine include the following topics.

Multi- or interdisciplinary research teams

- Developing multi- or interdisciplinary research teams with expertise in the life and physical sciences (e.g., developmental biologists, immunologists working with tissue engineers) and promoting translational research; and
- Encouraging cross-disciplinary discussions on broad issues, such as common standards, and providing opportunities for cross-training and education for emerging scientists.

Basic biology

- Understanding/controlling how stem cells differentiate, proliferate, and respond to physical stimuli in vitro and in vivo for the repair and regeneration of musculoskeletal tissues, including bone, cartilage, ligaments, menisci, tendons, and intervertebral discs;
- Reactivating developmental pathways of organogenesis—how cells self-assemble into complex musculoskeletal tissues in vitro and in vivo;

- Understanding the role of inflammation, senescent cells, and changes in immune systems on musculoskeletal tissue development, injury, repair, and regeneration; and
- Decoding how musculoskeletal tissues trigger and/or respond to vascularization, innervation, and immune signals.

Biological therapy development

- Designing and testing methods to deliver molecular, cellular, or gene-based therapies for repair of musculoskeletal tissues, and for joint disease treatment and prevention: of interest are in vivo strategies to deliver cells, genes, or biomolecules;
- Developing 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 preclinical studies in large animals;
- 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 versus differentiated cells such as chondrocytes; adult stem cells versus 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 musculoskeletal tissue repair and regeneration; and
- Expanding testing in preclinical models such as in large animal models for bench-to-bedside translation of regenerative medicine research.

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.

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 extracellular matrix 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.

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.

Enabling technologies

Methods and models

- Developing and testing minimally or noninvasive 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 3D 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 animal models of human disease.

Imaging and computational tools for regenerative medicine

- Developing real-time, minimally or noninvasive imaging modalities for in vivo monitoring of cell proliferation, differentiation, survival, migration, and integration;
- Developing real-time, minimally or noninvasive imaging modalities to monitor tissue-function repair and integration processes in vivo;

- Developing noninvasive imaging methods to measure functional capacity of tissue in small and large animal models and in humans; and
- Developing computational models to facilitate experimental design and effectively predict outcomes.

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 research directions include:

- Studying the relationship between regenerative medicine and rehabilitation;
- 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.

Preclinical and translational research into joint replacements

Implants such as those used in total hip and knee replacements have been shown to be effective tools to treat end-stage arthritis that has not responded to nonoperative treatment. These implants 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:

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/surface modifications that facilitate healing by stimulating implant integration and preventing infection;
- Using data-driven design approaches to improve implant durability and performance; and
- Developing unique 3D-printed orthopaedic implant materials.

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 (e.g., automated image recognition software 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.

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 analyses and other high-throughput genetic approaches to understand genetic risk factors for, and their relevance to, osteolysis.

Biochemical and imaging biomarkers and computational modeling

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, facilitate surgical decision making, 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 marker for assessing these conditions. In addition, when many different variables are collected, deducing connections among variables may require the aid of machine learning algorithms. These algorithms may result in computational models that can be used to subphenotype patients to improve diagnosis and treatment of musculoskeletal diseases. Moreover, leveraging the power of machine learning and automation of morphological grading of the tissues in the joints would enable the analysis of large sample sizes and assist the radiologist/clinician in the grading of images in a relatively short amount of time at significantly reduced cost. The box below describes an NIH effort to create a public resource to validate imaging and biochemical biomarkers for OA.

The Osteoarthritis Initiative (OAI): A Public-Private Partnership to Advance Biomarker Discovery

OA is the most common type of arthritis. It occurs when the tissue that covers the ends of bones in a joint is damaged, which allows the bones to rub together leading to pain, swelling, and loss of motion. A limited number of therapies exist for OA treatment. One barrier to the development of drugs that interrupt the underlying disease processes leading to OA is a lack of objective and measurable standards for disease progression for these new drugs. To overcome this problem, NIAMS, along with the National Institute on Aging (NIA), led the development of the Osteoarthritis Initiative (OAI), a nationwide, multicenter observational study to follow people who either have or are at risk for developing knee OA. This public-private partnership began more than a decade ago to gather and catalog longitudinal findings from a cohort of nearly 5,000 people with OA and healthy individuals.

All participant visits (baseline through 8 years follow-up) have been completed, which makes the OAI one of the largest and perhaps most important datasets in the history of OA research. The dataset contains clinical, genomic, patient-reported, and functional data; biological specimens; and X-ray and MRI images. The data are available free of charge at https://oai.nih.gov. In addition, genomic data from the ancillary Genetic Components of Knee Osteoarthritis (GeCKO) study, a genome-wide association study on the entire OAI cohort is available at the NCBI dbGaP website. Investigators can use this unique repository to track the natural history of knee OA across the complete spectrum of disease.

As NIAMS looks to FYs 2020-2024, extramural researchers are encouraged to examine OAI data to develop 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. These comprehensive datasets can be used to identify potential disease biomarkers and develop tools for measuring clinically meaningful improvements. The initiative also provides excellent training and research opportunities for early-stage investigators with limited funding to leverage this existing dataset and develop and test research hypotheses. In addition, OAI data serve as a novel resource for investigators with computational and machine learning expertise in other fields to apply big data methodologies to biomedical research.

For further information: https://www.niams.nih.gov/grants-funding/funded-research/osteoarthritis-initiative.

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:

Biomarker identification 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 candidate biomarkers at molecular and cellular levels to facilitate early detection of pre-OA;
- 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 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;
- Studying noninvasive biomarkers to facilitate early diagnosis and monitor treatment of musculoskeletal infections, including those surrounding implanted devices; and
- Developing in vivo molecular imaging technologies to facilitate the use of biomarkers to distinguish between diseased and healthy tissue (e.g., biomarkers and intra-operative molecular imaging methods to better assess joint tissues).

Resource development and application

- Implementing novel imaging modalities in preclinical and clinical studies;
- Applying existing and newly developed imaging technologies (for both acquisition and analysis) when studying disease and identifying possible imaging biomarkers associated with disease onset and progression;
- Employing existing resources, 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;
- Developing rigorous patient-based musculoskeletal computational models to assist with treatment planning and predict outcomes; and

- Developing supervised or unsupervised deep machine learning approaches for image processing, analyzing complex biostructural, biomechanical and functional models, enabling reliable and standardized disease screening, detection, and automatic analysis.

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). 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;
- Development and validation of patient-reported outcomes, including health-related quality-of-life measures, for different orthopaedic procedures;
- The use of registries, electronic medical records, and large databases to inform clinical studies;
- The development and use of unique clinical trial designs (e.g., pragmatic, adaptive);
- The importance of improved understanding of the role of psychological and social factors in musculoskeletal health; and
- Integration of social media and technology into clinical studies to improve research efficiency.

Conditions, diseases, and disorders

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 and his or her family.

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 (e.g., growth delay, osteoporosis, avascular necrosis, scoliosis).

Osteoarthritis

OA is by far the most common type of arthritis, which affects an estimated 27 million Americans age 25 years and older. Although this prevalence is high, it is expected to increase even further with the increasing prevalence of obesity and the aging population. OA can affect quality of life and the ability to work and perform basic activities of daily living. *Healthy People 2020* includes several objectives related to improved overall health and functioning of people who have arthritis. Current therapeutic regimens for OA are only partially effective and often have associated toxicities, and there are no disease-modifying drugs approved by the regulatory agencies at present. Further research is needed to develop effective therapies. Also see *Joint replacement* and *Behavioral and psychosocial research* sections for more information.

Broad areas of potential research directions related to risk factors include:

- Defining and stratifying OA risk factors, both modifiable and nonmodifiable, for incidence, morbidity, and mortality in individuals and in populations (nonmodifiable risk factors are age, sex, genetics and inherited traits; modifiable risk factors include weight and obesity, previous joint injury, 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;
- Emphasizing disease prevention by developing or modifying strategies, including behavioral and rehabilitative approaches, to avoid and prevent the development of OA after joint injury and to reduce the disability and functional limitations associated with OA onset and progression;
- Taking advantage of web-based and mobile technology to prevent poor outcomes after joint replacement surgery;
- Modulating triggers to prevent disease flares and prevent acute to chronic pain transitions;
- Subphenotyping OA patients, identifying responders and nonresponders to treatment to match a patient's phenotype to an appropriate effective treatment;
- 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;
- Identifying and developing solutions to barriers and enablers to enhance sustainability and adherence to exercise and weight loss interventions;
- Comparing the effectiveness of treatment programs to improve adherence and outcomes for patients;
- Identifying novel targets, developing novel drugs or repurposing existing drugs as DMOADs (disease-modifying osteoarthritis dugs);
- Pursuing innovative treatments (such as biologics and stem cells) to slow or prevent joint degeneration, and developing novel drug delivery approaches;
- Adopting modern clinical trial designs, for example, adaptive and pragmatic trials, to devise more efficient, less costly strategies for answering multiple questions about treatment effects and patient responses; and
- Establishing innovative approaches to using patient-reported outcome scores in decision making.

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 and for other surgical needs. 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 biomarkers and computational modeling* above, broad areas of potential patient-oriented research directions include:

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 postoperatively to see whether they can significantly increase implant osteointegration and decrease subsequent loosening;
- Testing long-term biocompatibility and wear properties of alternative-bearing surfaces;
- Standardizing criteria for determining therapeutic effects of nonsurgical interventions (such as drugs or rehabilitation strategies) to prevent or treat implant osteolysis (this will enable comparison of interventions across different studies); and
- Developing and adapting patient-reported outcomes for different orthopaedic joints.

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 effective 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.

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 nonsurgical therapies for common causes of low back pain has yielded important results. 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. Recently, NIAMS established the NIH Back Pain Consortium Research Program (see *Musculoskeletal pain* below), a patient-centric program to promote understanding of the causes of and treatments for chronic low back pain.

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;
- Assessing basic/clinical biological mechanisms associated with spinal disorders and their related pain syndromes;
- Acute and chronic back pain (in regions spanning the cervical, thoracic, and lumbosacral spine);
- 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.

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 one of the leading causes of death after the first year of life. 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 nonoperative techniques and rehabilitation after fractures or skeletal trauma will improve patient outcomes, enhance the lives of patients and their caregivers, and facilitate return to the workforce.

Broad areas of potential research directions include:

Prevention:

- Elucidating mechanical forces that contribute to or cause joint injuries (e.g., ACL tears, herniated discs) and understanding the consequences of cumulative trauma disorders of soft tissues (such studies could be useful for preventing injuries and developing protective devices for preventing these injuries);
- Defining the role personalized medicine can play in maintaining bone and joint health;
- Developing injury prevention programs that are cost effective, easily applicable, and readily disseminated to diverse populations;

- Preventing childhood/adolescent injuries (including sports related injuries); and
- Assessing effectiveness of strategies for preventing soft tissue injuries in children and adults.

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.
- Developing and validating measures that better assess and aid 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;
- Enhancing fracture healing through bone grafts and other implant materials, including the use of growth factors;
- Developing methods to repair damage to cartilage, connective tissue, and fibrocartilaginous tissues (including menisci) related to fractures in the joint area;
- 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 and developing strategies to diagnose and treat symptomatic rotator cuff tears;
- Exploring the natural history of rotator cuff tears to understand why some are more symptomatic than others; and
- Implementing strategies to standardize clinical studies of interventions that influence fracture and soft tissue healing, using both objective and subjective parameters.

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.

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

Physical activity requirements

- Acquiring better understanding of how particular fitness requirements vary by 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 of which types of exercise are optimal for promoting musculoskeletal health.

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 athletes (including repetitive motion disorders of the rotator cuff); and
- Prevention of secondary injuries (in shoulder and ACL, including reinjury or contralateral injury).

Treatment and rehabilitation

- Applying physical medicine and rehabilitative strategies to soft tissue injuries to restore maximal function and enhance return to sport;
- 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”);
- Developing musculoskeletal “prehabilitation” programs to improve functional outcomes after surgery;
- Developing state-of-the-art technologies to aid in the diagnosis and treatment of musculoskeletal injuries (including wearable devices and ultrasound-guided interventions); and

- Developing and optimizing the clinical use of biologics (including stem cells, platelet rich plasma, bone marrow, and fat cells) as treatments for musculoskeletal injuries. Additional information on the use of biologics in clinical orthopaedics can be found in the consensus report from an NIAMS-funded American Academy of Orthopaedic Surgeons meeting in 2018.

Musculoskeletal pain

Musculoskeletal pain takes many forms in children and adults. From acute and chronic back pain to tendonitis, myalgia, joint pain, stress fractures, and growing pains, there are many unmet needs. These include an improved understanding of the biological underpinnings of the origins of pain and discovery, development, and testing of new nonaddictive pain treatments. For example, more rigorous studies are needed to improve our understanding of the mechanisms of chronic low back pain, improve its diagnosis and treatment, and prevent its transition from acute to chronic status. To improve understanding of chronic low back pain, NIAMS developed the NIH Back Pain Consortium Research Program (BACPAC), part of the NIH HEAL initiative (Helping to End Addiction Long-term^{SM}). This research program is a patient-centric translational research initiative that will address the need for effective and personalized therapies for chronic low back pain by probing the biomedical mechanisms in a biopsychosocial context using interdisciplinary methods and innovative technologies.

Broad areas of potential research directions include:

- Using advanced genetic, molecular, neurobiological, behavioral, and imaging techniques to identify mechanisms, genetic and molecular pathways, and biological processes of musculoskeletal pain;
- Exploring biopsychosocial mechanisms of pain, including sensory, cognitive, and affective components of pain, and determining the relationship between tissue damage and the experience of pain;
- Developing novel animal models that are highly relevant to human musculoskeletal pain conditions;
- Developing novel technologies, including sensor-driven implantable devices and wearable technologies, to target peripheral pain pathways, detect cellular and structural changes of tissues and organs, and record patient functional outcomes;
- Defining and supporting best practices for pain management using nonpharmacological and integrated therapies for specific musculoskeletal pain conditions;
- Examining different components and effectiveness of self-management strategies for chronic pain; and

- Advancing the development of new nonaddictive pain treatments by building mechanistic research centers, clinical trials networks, and pursuing public-private partnerships for data sharing.

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 may shed light on complex mechanisms involved in pathogenesis.

Broad areas of potential research directions include:

- Assessing the willingness of individuals belonging to racial and ethnic subpopulations 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 for behavior modification leading to desired health outcomes (e.g., weight loss).

MANAGEMENT, SCIENTIFIC STEWARDSHIP, AND ACCOUNTABILITY

Through responsible management and scientific stewardship NIAMS promotes exploration of a broad spectrum of highly meritorious research. Several of the Institute's current activities related to management, stewardship, and accountability are described in the following sections. The Institute will continue to support and promote these activities over the next 5 years while looking for new opportunities to promote scientific stewardship and accountability.

An important component of management at NIAMS is a planning and priority-setting process that incorporates input from the research community. NIAMS also considers assorted relevant data when making decisions about scientific programs and conducts quantitative or qualitative assessments of programs and research topics, as needed, to guide future activities.

NIAMS also implements trans-NIH activities to enhance management, stewardship, and accountability. For example, these include efforts to reduce administrative burden on investigators, proactively manage risks that might impede the agency's mission, and ensure that NIAMS-funded research is conducted with a high degree of scientific rigor and in accordance with ethical standards.

NIAMS seeks to ensure the continuity and progress of research in its mission areas through training and career development programs for outstanding early-stage investigators and through dedicated funding for studies with the potential to positively shift scientific paradigms. The Institute fosters a vibrant research environment through investments in key research resources and facilitates access to those resources and data through partnerships with a wide array of public and private organizations in mission-relevant areas.

Accountability for taxpayer funds is a key guiding principle of NIAMS activities. The Institute seeks to ensure integrity, accountability, and transparency in the grant award and administration processes. Program Officers and Grants Managers work closely together to accomplish this goal. One group is responsible for the fiscal and administrative management of a grant award and the other for the scientific and programmatic aspects. Staff work closely with awardees to ensure effective management and oversight, while also providing excellent customer service and guidance.

Pre-award processes assure that established administrative, ethical, and financial requirements are met, including protection of human and animal subjects, monitoring of conflicts of interest, promoting data sharing, and requiring the responsible and ethical conduct of research. Post-award monitoring assures that projects are managed appropriately and that funds are being spent

in a prudent and effective way. Grant closeout procedures assure final progress and expenditures are reported and that results are available to the public.

Further, the Institute is committed to supporting research that reflects the diversity of the Nation so that the results of NIAMS-funded research benefit all members of society. NIAMS also prioritizes outreach to the public and broad dissemination of research findings to encourage their implementation to improve health.

Priority Setting

Like the rest of NIH, the process of setting NIAMS's research priorities balances opportunities presented by the best science, public health needs, and the unique ability of the Institute to address challenges in human health that would otherwise go unmet. NIAMS's long-standing priority setting process is predicated on three activities:

- Submission of investigator-initiated research applications;
- Peer review to identify the most promising research projects; and
- Stakeholder input on research gaps and opportunities.

Going forward, NIAMS will continue to rely on these priority-setting activities and will seek out opportunities to enhance them.

Submission of investigator-initiated research applications

NIAMS believes that investigator-initiated research is a key part of efforts to improve the health of people who have rheumatic, musculoskeletal, and skin diseases. The term "investigator-initiated" means that a researcher bases his or her grant proposal on any area of science that NIAMS supports instead of waiting for the Institute to publish a special funding opportunity announcement seeking applications on a specific topic. This has the dual advantages of positioning the Institute to receive the best, most interesting and promising ideas from the research community and of allowing investigators the creativity and freedom to explore the topics that they are most interested in and best poised to address.

The NIAMS portfolio covers a broad and diverse spectrum of research and training responsibilities and NIAMS does not set aside particular pools of money for disease- and tissue-specific topics within its mission. This provides the Institute the flexibility to fund the most outstanding research grant applications regardless of scientific discipline and to fund as many as possible of the myriad needs and opportunities across the broad base of science within its mission.

Peer review to identify the most promising research projects

The decision to fund an application is based on the assessment of scientific merit by a peer review group and on the relevance of the proposed work to the Institute's scientific and health priorities. While the Institute Director ultimately is responsible for deciding which applications to fund, the assessments of expert scientists and lay representatives from around the country factor heavily into the decision-making process.

Peer reviewers' judgments of scientific merit are expressed in "priority scores" and in percentile rankings derived from these priority scores. At any point in a given fiscal year, budgetary projections are based on awarding funds to applications with rankings better than a certain percentile, sometimes referred to as the "payline." However, applications that address topics of particular relevance to the Institute's scientific and health priorities may be considered for awards even if their assigned scores and percentile rankings would not qualify for funding under the current payline. Normally, a small portion of each year's budget is reserved for such "discretionary" or "select pay" awards. Projects to be funded on this basis are recommended by Institute staff or Advisory Council members. Applicants may not apply for select pay consideration. Final decisions are made by the Director, NIAMS, following staff discussion.

Rarely, NIAMS receives an application that is within the Institute's payline but is deemed to be of low program priority. In such instances, these cases are discussed in depth with members of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council before the Institute Director makes a final funding decision. An application can be considered low priority for many reasons, including (but not limited to) redundancy with other projects or concerns about the ultimate relevance of the proposed study's results or about the scientific premise.

NIAMS publishes its funding plan for each fiscal year on an annual basis on the NIAMS website.

Stakeholder input on gaps and opportunities

NIAMS routinely invites input from the extramural scientific community and members of the broader public by issuing Requests for Information or through listening sessions with researchers and NIAMS Coalition members. Such activities have shaped this Strategic Plan and other NIAMS initiatives and programs, both large and small.

NIAMS has a history of carefully considering input from the National Arthritis and Musculoskeletal and Skin Advisory Council before making significant changes to existing programs and often presents data-driven analyses to the Council when soliciting its input. Recent examples include the decision to change the eligibility criteria for the Supplements to Advance

Research (STAR) program (discussed below) and the Small Grant Program (R03). Council input also has shaped Institute policies regarding the clinical trial applications that it considers and the structure of the NIAMS Centers programs.

Workforce Recruitment, Development, Retention, and Diversity

Biomedical and behavioral research is a human endeavor and NIAMS is committed to keeping the scientific workforce pipeline strong and diverse. Through ongoing assessment of needs and opportunities, NIAMS has maintained a multidimensional approach to training and career development. Nurturing a healthy pipeline of biomedical researchers focused on the diseases and disorders that are included within the NIAMS mission is critical to advancing scientific progress.

Many research questions important to the NIAMS mission will require multi- and interdisciplinary contributions and 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 multidisciplinary or interdisciplinary projects, as appropriate. In addition, NIAMS recognizes a need to incorporate additional areas of expertise, such as data science, biomedical engineering, clinical trial design, and patient engagement, to ensure the effective translation of scientific discoveries into health benefits. To meet these needs, NIAMS encourages new approaches to ensure individuals with nontraditional areas of expertise are represented in research teams.

Going forward, NIAMS will continue to leverage existing and emerging programs and mechanisms to ensure there is a robust and diverse pipeline of researchers and clinician-scientists to carry the Institute's mission forward. The Institute remains interested in developing partnerships with research and professional societies or patient organizations to encourage trainees and clinicians to enter the scientific research workforce or to maintain research efforts as investigators make critical career-stage transitions.

Building and maintaining the workforce

Attracting and maintaining a robust, diverse scientific workforce is critical to the NIAMS mission. The Institute participates in many trans-NIH programs to encourage and foster the development of early-stage investigators as they pursue research projects on arthritis, rheumatic diseases, musculoskeletal conditions, and skin diseases. Predoctoral fellows in Ph.D. or formal dual-degree programs, such as M.D./Ph.D. programs, 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 approaches to encourage clinicians to enter into or continue their research careers. A suite of mentored career development awards aid emerging clinician-scientists as they develop independent research careers by providing resources and protected time for research. For example, the NIH Mentored Clinical Scientist Research Development Award (K08) supports clinicians for an intensive experience in basic and translational research. In addition, the NIH Mentored Patient-Oriented Research Career Development Award (K23) is targeted to individuals with a clinical doctoral degree who intend to focus their research on human studies and work directly with people. NIAMS also supports clinical K08 and K23 physician-scientists by offering special webinars and meetings to allow them to engage with NIAMS leadership and extramural staff. The long-term goal of these meetings is to enhance, encourage, and enable "K-awardees" to navigate critical transitions and retain them in independent research careers.

Clinician-scientists are also encouraged to apply to the NIH Loan Repayment Program (LRP). The escalating costs of advanced education and training in medicine and clinical specialties have led some scientists to abandon research careers for potentially more lucrative industry or private practice careers. The LRP counteracts that financial pressure by repaying a portion of the researcher's qualified educational debt in return for a commitment to engage in specified NIH mission-relevant research.

Several NIH and NIAMS programs address the development and retention of mid-career scientists. For example, the NIH Mid-career Investigator Award in Patient-Oriented Research (K24) provides protected time for mid-career clinicians to conduct research while serving as mentors for junior clinical investigators, particularly K23 grantees. The K24 award is intended to stabilize the careers of these investigators as they continue their research, directly interacting with patients while simultaneously supporting the development of the next generation of clinical researchers.

NIAMS also offers the Supplements to Advance Research (STAR) program to provide additional support for investigators to pursue innovative and high-risk research within the broader scope of a current NIAMS-funded, peer-reviewed research project. STAR provides supplemental funding to investigators who have renewed their first NIAMS R01 grant and aids investigators as they work to expand a single, structured research project into a broader multi-faceted research program. The STAR program allows space for flexibility, innovation, and risk-taking related to the research area of the parent R01 and is optimized to support principal investigators as they develop challenging, creative, and innovative scientific endeavors that will sustain a career.

Workforce diversity

A growing body of evidence shows that workforce diversity is associated with creativity and innovation—characteristics that are essential for tackling complicated research questions. As the Advisory Committee to the NIH Director Working Group on Diversity in the Biomedical Research noted in its 2012 report, a workforce that better resembles the population that it serves can provide stronger ties with global research networks and improve engagement of underrepresented racial and ethnic minorities in community-based studies. Many rare diseases and conditions within the NIAMS mission cannot be investigated adequately without international research teams and patient cohorts, making this a high priority for the Institute. In addition, many forms of arthritis and musculoskeletal and skin diseases disproportionately affect Americans from minority racial or ethnic backgrounds. Fostering a research community that includes diverse leaders is expected to improve health equity across NIAMS disease areas.

More than half of the U.S. population under 18 years of age will soon be non-white and many of these young people will aspire to enter scientific or biomedical careers in the future. NIAMS is committed to making biomedical research careers more attractive to students from traditionally underrepresented backgrounds. In addition, NIAMS encourages the inclusion of scientists from underrepresented groups in leadership teams and advisory groups to leverage diverse perspectives and improve the likelihood of generalizability of research results.

NIAMS participates in NIH programs designed to attract and encourage individuals from underrepresented populations to pursue research careers by providing a continuum of research training opportunities, from high school to higher education faculty levels. NIAMS recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, and clinical research workforce through the Diversity Supplement Program. The overall goal of the program is to improve the diversity of the research workforce by recruiting and supporting students, postdoctoral researchers, and eligible investigators from diverse backgrounds, including those from groups that have been shown to be underrepresented in health-related fields.

Next Generation Researchers Initiative

NIAMS has a long-standing history of participation in trans-NIH initiatives and policies designed to facilitate early-stage investigators (ESIs) as they transition to independent careers by obtaining their first major NIH award. In alignment with the NIH-wide Next Generation Researchers Initiative (NGRI), ESI status is considered during review and ESIs are given special funding consideration. In addition, the Institute has established processes to give individual attention to meritorious applications from investigators who lost, or are at risk of losing, all NIH research support, or investigators supported by only one active award. NIAMS will revisit these

policies annually to ensure they are reaching programmatic goals and to maintain alignment with evolving trans-NIH NGRI policies.

Innovation

NIAMS leadership understands that innovation is the basis of scientific progress. It is nearly impossible to predict from where the next research direction or great scientific breakthrough will emerge; hence the Institute's strong commitment to investigator-initiated research and the process of peer review to identify meritorious proposals. Nevertheless, challenging the status quo is often inherently risky, and when resources are constrained review tends to be conservative, supporting safe bets rather than high risks. NIH data have shown that of the five standard peer review criterion scores, "innovation" is not a primary predictor of funding for R01 applications.

NIAMS and NIH have implemented programs to promote innovative research concepts and the pursuit of scientific hypotheses that could steer science in new directions. For example, the NIH Common Fund's High-Risk, High-Reward Research program supports exceptionally creative investigators pursuing highly innovative research with the potential for broad impact in biomedical or behavioral science. The program's four constituent NIH Director's awards provide a diverse set of funding opportunities for outstanding investigators at all career stages. NIAMS encourages the pursuit of its mission areas though these opportunities.

Discoveries in biomedical and behavioral research are often not ready for immediate clinical application or commercial development. The NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs are one mechanism available to address this gap. The SBIR/STTR program is one of the largest sources of research funding for small businesses and startups and it supports and encourages the translation of research discoveries and novel technologies into innovative commercial products. Awards provide 6 months (SBIR) or 1 year (STTR) of support for proof-of-concept testing and 2 years for research and development. The program encourages small businesses to develop new technologies and products with potential for commercialization across health domains. The NIAMS SBIR/STTR program aims to facilitate the translation of basic discoveries into commercial applications within the Institute's mission areas.

In addition, NIAMS has initiated the Research Innovations for Scientific Knowledge (RISK) program. This novel mechanism focuses on innovative research within the NIAMS mission by encouraging applicants to pursue unusual observations, test imaginative hypotheses, investigate creative concepts, and build groundbreaking paradigms that deviate significantly from current prevailing theories or practice. RISK is particularly designed to encourage the submission of projects that are considered too risky, premature, controversial, or unconventional for other NIH mechanisms. While the program's focus is on scientific innovation, the review and funding of

proposals is also innovative, including a novel "anonymous" pre-application review phase prior to submission of an application for funding consideration. In addition, funded awards provide support for up to 2 years to perform critical experiments that rigorously test the proposed concept. The outcomes of these experiments are a central factor in determining whether the project will continue on to the second phase with additional support to further validate and explore the innovative concept. Through the RISK initiative, NIAMS supports bold and eclectic ideas and specifically fosters innovative proposals in concert with other NIH research project mechanisms.

The 21st Century Cures Act provides NIH with critical tools and resources to advance biomedical research across the spectrum, from foundational basic research studies to advanced clinical trials of promising new therapies. As part of the law, multiyear funding for four highly innovative scientific initiatives was authorized, including the *All of Us* Research Program, the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the Cancer Moonshot℠, and the Regenerative Medicine Innovation (RMI) Project. NIAMS participates in these funding opportunities where there is overlap with the NIAMS mission. For example, NIAMS partnered with the National Cancer Institute and the National Institute of Allergy and Infectious Diseases on Cancer Moonshot efforts to clarify the relationship between cancer, autoimmunity, and immunology, and provided supplements to existing grants for research collaborations on immune-related adverse events associated with cancer immunotherapy. NIAMS also actively participated in RMI program funding opportunities with the goal of accelerating regenerative medicine discoveries related to NIAMS mission and enhancing support for innovative clinical research using adult stem cells while promoting the highest standards for carrying out scientific research and protecting patient safety. NIAMS plans to continue participation in these unique programs.

Research Partnerships

NIAMS works closely with other NIH Institutes, Centers, and Offices to leverage their unique strengths and avoid duplication of efforts. The Institute continues to encourage investigators to leverage research resources generated through the NIH Common Fund or other trans-NIH programs. The Institute also works to ensure that NIAMS-supported researchers are represented in trans-NIH meetings that are important to our communities. In turn, NIAMS includes researchers supported by other NIH Institutes, Centers, and Offices in NIAMS-led meetings, as appropriate.

The breadth of the NIAMS mission and its importance to the Nation's health is evidenced in the involvement of Institute staff in the development of trans-NIH and interagency priority-setting documents, such as the following:

- Action Plan for Lupus Research (2015)
- 2015 Action Plan for the Muscular Dystrophies
- National Institutes of Health Research Plan on Rehabilitation (2016)
- Federal Pain Research Strategy (2018)
- 2019-2023 Trans-NIH Strategic Plan for Women's Health Research
- Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention (2019)
- Healthy People 2020 and 2030

Investigators are encouraged to explore these and other resources, as well as the NIH and NIAMS Strategic Plans as they look for exciting ideas and opportunities to pursue. The most up-to-date list of NIH-wide strategic plans can be found at https://report.nih.gov/strategicplans/index.aspx.

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) and works closely with the NIH Office of Behavioral and Social Sciences Research. These interactions allow the Institute to share information about NIAMS-funded research efforts and advances and to form partnerships with other NIH components in areas of common interest.

Below are a few historical examples of partnerships that NIAMS has led or contributed to. The resulting data sources are available for arthritis and musculoskeletal and skin researchers to leverage as they develop scientific proposals over the next 5 years.

- In the early 2000s, NIAMS and the National Institute on Aging organized the Osteoarthritis Initiative (OAI), a public-private partnership that included several NIH Institutes, Centers, and Offices, the U.S. Food and Drug Administration (FDA), and four pharmaceutical companies. Today, OAI is a publicly available research resource containing clinical data, images and specimens from more than 4,500 participants, many of whom have been involved in the study for more than a decade. Researchers are welcome to use OAI resources 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. They also can use OAI to identify potential disease targets and develop tools for measuring clinically meaningful improvements.

- In 2014, NIAMS joined with the National Institute for Allergy and Infectious Diseases (NIAID) to lead the Accelerating Medicines Partnership (AMP) program in rheumatoid arthritis and systemic lupus erythematosus (RA/SLE). AMP is an initiative sponsored by NIH, biopharmaceutical companies, and several nonprofit organizations to transform the

current model for developing new diagnostics and treatments. The data generated from cutting-edge technologies are being made publicly available for other researchers to interrogate through the NIAID-sponsored Immunology Database and Analysis Portal (ImmPort), while genomic data are available through NIH's database of Genotypes and Phenotypes (dbGaP). In the coming years, results from the projects are expected to improve understanding of the molecular and cellular basis of RA and SLE and of heterogeneity among patients with these diseases, providing new opportunities for effective, personalized treatments. The data from the project will continue to be an important resource for biomedical and clinical research and a potential basis for future research collaborations.

- Until Common Fund support ended in 2014, NIAMS managed the NIH Patient Reported Outcomes Measurement Information System (PROMIS®), a collaborative initiative among many NIH Institutes, Centers, and Offices. The purpose of the initiative was to develop psychometrically robust ways of measuring issues that affect the day-to-day lives of patients, such as pain, fatigue, physical functioning, emotional distress, and social role participation across a variety of chronic diseases. These measurement tools can be used to bring patients' voices and experiences into clinical research so that interventions being developed by the research community will, in addition to improving clinical parameters, address quality of life. Component questions of the PROMIS instrument have been rigorously tested in culturally and ethnically diverse populations. They can be used to measure changes in patient-reported outcomes over time and in response to treatments. A 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. For more information about PROMIS®, see Patient-Centric Approaches to Health and Disease in the section on Cross-cutting Scientific Themes.

- Over the next five years, the Molecular Transducers of Physical Activity Consortium (MoTrPAC) will be releasing data investigators can use to identify the molecules that protect against bone, joint, and muscle deterioration and that preserve physical function. MoTrPAC's goal is to assemble a comprehensive map of the molecular changes that occur in response to physical activity and, when possible, relate these changes to the benefits of physical activity. This map will contain the many molecular signals that transmit the health effects of physical activity and will indicate how they are altered by variables such as age, sex, body composition, fitness level, and chronic exposure to exercise. Information about MoTrPAC resources, animal and clinical protocols, and the potential for ancillary studies are available at www.motrpac.org.

- Looking to the future, the *All of Us* Research Program's one million person cohort will provide many opportunities regarding a range of NIAMS-related health issues. Immune

and inflammatory diseases, musculoskeletal and movement disorders, and chronic pain conditions are among the topics that comprise the program's scientific framework. Scientific opportunities afforded by *All of Us* include studies of gene and environment interactions, pharmacogenomics, biomarkers, and mobile health technologies. Data will be available through the *All of Us* Research Hub.

Inclusion of Diverse Populations as Participants in Biomedical Research

As stated previously, many diseases that fall within the NIAMS mission exhibit sex, racial, ethnic, and other disparities. Given what is known about the populations affected by these diseases, it is critical to ensure that the research the Institute supports appropriately includes a diverse group of participants. NIH and NIAMS are committed to the inclusion of women and minorities in all NIH-funded clinical research. This is demonstrated through implementation of the NIH Revitalization Act of 1993 (Public Law 103-43), which requires inclusion of women and members of minority groups and their subpopulations in NIH-funded clinical research, including clinical trials, 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.

The 21st Century Cures Act (Public Law 114 -255), enacted in 2016, introduced new requirements related to inclusion of participants in clinical research. As a result, NIH updated its policy on the Inclusion of Women and Minorities as Subjects in Clinical Research. Additionally, NIH revised its Inclusion of Children Policy, which is now called the NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan, to ensure that clinical research includes individuals of all ages unless there is an appropriate justification to do otherwise.

In addition to the efforts described above that relate to clinical research, NIH also encourages enhanced attention to sex as a critical factor in basic and preclinical studies. In 2015, the agency announced a policy on Consideration of Sex as a Biological Variable to foster research that improves understanding of the biology underlying sex differences and provides knowledge to improve the health of women, men, girls, and boys. NIAMS supports NIH's overarching efforts on studying sex and gender, which call on researchers to take sex into account as they develop their research questions, design experiments, analyze data, and report results.

Performance Measures and Assessment

NIAMS, like NIH as a whole, supports research with the ultimate goal of curing disease and improving overall health. However, significant time elapses between basic discovery and development of clinical applications. Scientific discovery often involves years to decades worth of incremental advances that are critical to achieving the ultimate goal of turning discovery into health. While a direct link can sometimes be drawn between specific funding and an improvement in health, most often the story is complex. Thus, determining the extent to which NIAMS has met the objective of improving health can be a challenge. Furthermore, over the course of a 5-year period the scientific field can advance and evolve in many unanticipated ways. As noted in the Director's Message, these unexpected breakthroughs also serve as indicators of progress and are a successful outcome of support. With this in mind, NIAMS will adopt a mixed methods approach that balances quantitative and qualitative methods to examine outputs and outcomes from this Strategic Plan for FYs 2020-2024.

An important management component at NIAMS is a planning and priority-setting process that incorporates input from the scientific community. The Institute's focus on investigator-initiated research applications and identification of the most promising research projects through peer review requires performance measures that reflect the full scope of the NIAMS mission and the work funded based on these processes. In addition to the investigator-initiated peer-review process, NIAMS uses evidence-based information when making decisions about scientific programs and conducts quantitative or qualitative assessments of programs and research topics to guide activities. With a growing evolution in the use of evidence to inform policy decisions, the performance measures and metrics NIAMS uses may be adjusted and should be evaluated regularly to ensure they are providing the information needed to guide priority setting efforts. This section reiterates some of the ways in which NIAMS currently uses data to inform decision making and discusses several potential measures that NIAMS may use in the future to assess its research portfolio and progress toward its scientific objectives of advancing and accelerating research within its mission.

Investigator-initiated research supported by NIAMS, through funding mechanisms such as R01 awards, is conducted across the Institute's disease- and tissue-specific mission areas described in this plan. Working with partners across NIH, such as the Office of Portfolio Analysis, Office of Evaluation, Performance, and Reporting, and other NIH components, NIAMS will identify appropriate measures and tools for a particular portfolio analysis and evaluation. For investigator-initiated research, such assessments could be used to evaluate and monitor innovation that results from this funding pool or to help guide select pay decisions and gauge their effects.

NIAMS also supports targeted programs that focus on early-stage investigators, high-risk research with potential to drive innovation, or establishing research resources for use by the larger scientific community, such as the OAI and AMP. For targeted efforts, NIAMS uses evaluation tools and data-driven assessments to help inform the creation of new programs and to revise and re-issue funding opportunity announcements for existing programs. Several examples of assessments of targeted programs are highlighted throughout this Strategic Plan. The section on *Priority Setting* notes that program assessments have shaped changes to the NIAMS Supplements to Advance Research (STAR) program and the Small Grant Program (R03). The section on *Advancing and Accelerating Muscle Biology and Disease Research* describes an evaluation of the Wellstone Centers program and how that effort is being used to identify program changes that could enhance efforts to achieve the Centers' goals. Assessment of targeted programs over the short- and long-term will rely on both quantitative and qualitative measures and may include analysis of career trajectories for trainees and early-stage investigators or significant advances spurred by targeted program efforts. Moving forward, NIAMS will continue to use approaches that may include, but are not limited to, an analysis of outputs (e.g., publications, development of new methods), outcomes (e.g., significant conceptual advances, stories of discovery, influential papers), and bench-to-bedside translation resulting from supported research.

Consistent with the Institute's emphasis on collecting stakeholder input, NIAMS will continue to hold roundtable discussions to assess research gaps and opportunities in specific mission areas, cross-cutting scientific themes, and clinical research efforts. NIAMS may also engage the community through listening sessions with researchers and NIAMS Coalition members to identify emerging research directions that could benefit from Institute encouragement.

Finally, NIAMS will work to ensure that the performance measure development and implementation process is incorporated across the Institute. Defining success prior to the launch of a new concept will facilitate gathering data to measure progress and allow identification of adjustments to improve performance.

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, and skin. Sharing information about research progress and conducting outreach to multiple audiences are essential components of the NIAMS mission. The Institute is committed to communicating research advances to all segments of the public.

Information dissemination

The Institute is dedicated to working closely with grantees and their institutions to disseminate research findings to constituents via multiple venues. Key priorities include:

- Enhance access to reliable, audience-appropriate health information in multiple languages and formats, with an emphasis on electronic offerings (see *Information Dissemination and Outreach Resources FAQs* section below); and
- Raise awareness of NIAMS-supported research through plain language materials that are widely disseminated through 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 (NRC). Both clearinghouses distribute health information materials to patients, allied health professionals, 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 NRC provides an important link to resources and information on metabolic bone diseases including osteoporosis, Paget's disease of bone, and osteogenesis imperfecta. It is supported by NIAMS, with contributions from the National Institute on Aging, the National Institute of Diabetes and Digestive and Kidney Diseases, and the NIH Office of Research on Women's Health.

Social media has increasingly become a primary avenue through which people receive news and information, as well as a main vehicle for communicating 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 information, recently published research articles, news and announcements, training and funding opportunities, and other information and resources. NIAMS hosts live social media events with other NIH Institutes, Centers, and Offices and professional and voluntary organizations to address timely health topics. NIAMS regularly posts videos on its YouTube channel and scientific images on its Flickr photo stream. NIAMS will continue to evaluate efforts to reach more constituents through social media channels and to explore integration of other social media tools to target and increase direct interaction with diverse audiences.

Information Dissemination and Outreach Resources FAQs

What sort of plain-language materials 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 materials in easy-to-read English formats, as well as in several other languages including Spanish, Chinese, Korean, and Vietnamese. A separate Spanish web portal and Asian languages web section let visitors easily access information in different languages.

How can a constituent stay informed about NIAMS activities?

The Institute produces several e-newsletters that are available by easy online subscription. These include the *NIAMS Update*, an electronic digest for those interested in the latest NIAMS/NIH-supported scientific news and resources on diseases of bones, joints, muscles, and skin. The Institute also develops the *NIAMS Community Outreach Bulletin*, an online digest designed to inform community organizers and health professionals about resources for diverse audiences. In addition, NIAMS disseminates *Honoring Health: Resources for American Indians and Alaska Natives*. Institute updates are also available through several social media channels.

Where can someone find answers to questions about NIAMS, its research, or its health information?

The NIAMS clearinghouses have bilingual Spanish/English information specialists who respond to public inquiries about topics under the NIAMS purview. Assistance is easily available via phone, email, or letter (see Contact Us).

Looking ahead, NIAMS will continue to respond to the increased demand for online health and research information. The NIAMS website has been redesigned to be easily viewed on a phone, tablet, or computer. This key outreach platform will be regularly updated and refined based on user metrics and content development, in alignment with the NIAMS mission.

Outreach

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

- Increase the visibility of NIAMS as a leading resource for information on diseases and conditions of bones, joints, muscles, and skin; and

- Expand awareness among scientists and students at all education levels about career 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 research advances and related developments, as well as to foster dialogue on future paths and directions of NIAMS-funded research. The Coalition is an independent consortium of professional and voluntary organizations that works to raise awareness about NIAMS research into the basic understanding, causes, treatment, and prevention of diseases of bones, joints, muscles, and skin. The Coalition plays a vital role as a voice of the researchers and patients for whom NIAMS works. The Institute will continue to engage regularly with Coalition partners through teleconferences and webinars, in-person meetings, and presentations at professional and voluntary meetings.

NIAMS will continue its Community Outreach Initiative to ensure that resources reach diverse populations. Through development and distribution of an e-newsletter, a social media toolkit, and other materials, health care providers and community organizers in multicultural communities nationwide receive access to health information and resources about health conditions that affect bones, joints, muscles and skin. In addition, NIAMS has implemented a Language Access Plan as part of NIH-wide efforts to help ensure that people who have limited English proficiency have meaningful access to all NIAMS programs and activities.

To broaden outreach to underrepresented groups, NIAMS is taking an active role in leading the NIH American Indian/Alaska Native (AI/AN) Health Communications and Information Work Group, a collaboration that represents more than 20 NIH Institutes, Centers, and Offices. The working group partners with the Indian Health Service (IHS) and the Administration on Aging/Administration for Community Living to develop and disseminate health information to IHS community health representatives and Title VI grantees nationwide.

APPENDICES

Appendix 1: Overview of the Development Process

The NIAMS Strategic Plan for Fiscal Years (FYs) 2020-2024 continues to build on the foundation of the Institute's previous long-range plans. It also includes new additions to feature four broad cross-cutting scientific themes, selected based on input from the community, that are relevant to all, or most, of the disease- and tissue-specific topics within the NIAMS mission and to address NIH and NIAMS initiatives related to management, scientific stewardship, and accountability.

NIAMS solicited comments on how the NIAMS Long-Range Plan for FYs 2015-2019 should be updated via a Request for Information (RFI) (Appendix 2) and gathered additional information through listening sessions with the NIAMS stakeholder communities.

The RFI was posted on the NIAMS website and in the *NIH Guide for Grants and Contracts*, and it encouraged feedback from researchers in academia and industry, health care professionals, patient advocates and health advocacy organizations, scientific and professional organizations, Federal agencies, and other interested members of the public. Information about the RFI was shared in emails to grantees, NIAMS Coalition members, and NIH components to encourage broad response. The comment period spanned 6 weeks. Respondents were asked to provide input on research needs and opportunities that should be modified because of progress over the last 5 years, emerging research needs and opportunities that should be added, and cross-cutting scientific themes or research-related themes common to all, or most, of the disease- and tissue-specific topics within the NIAMS mission that should be included. General comments were also encouraged.

In November and December 2018, seven listening sessions were held with more than 100 individuals. The listening session participants consisted of researchers and patients representing systemic rheumatic and autoimmune diseases, skin biology and diseases, muscle biology and diseases, bone biology and diseases, joint biology, diseases, and orthopaedics, as well as members of the NIAMS Coalition, a group of more than 90 professional and voluntary organizations interested in the Institute's mission areas. Six of the listening sessions were held via conference calls. The seventh session was an in-person meeting with established researchers and professional and voluntary organization representatives who attended the NIAMS K Forum for Clinical Mentored K Awardees. All listening session 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 new section of the plan on cross-cutting scientific themes. Part of the discussion was also devoted to health disparities and training and career development. Further, participants in the listening session with the NIAMS Coalition provided input on how the new NIAMS Strategic Plan for FYs 2020-2024 could be structured to be most useful to NIAMS varied stakeholders. Updates on the development of the NIAMS Strategic Plan for FYs 2020-2024 were provided at the September 2018 and February 2019 Advisory Council meetings. In February 2019, the NIAMS Acting Director convened a Working Group of the Advisory Council to review the draft plan, which was presented to the Working Group and Advisory Council in May 2019. The NIAMS Advisory Council Working Group for the Strategic Plan discussed the draft plan via a conference call in May 2019 and reported their findings and recommendations at the June 2019 Advisory Council meeting. Feedback from the Working Group and Advisory Council was incorporated into the draft plan after the meeting.

The Institute then issued a second RFI to invite public comments on the revised draft plan. The RFI was published in the *NIH Guide for Grants and Contracts* and information posted on the NIAMS website (Appendix 2). The comment period spanned 3 weeks. In addition to the outreach efforts similar to those associated with the first RFI, the Institute also issued a *Federal Register* Notice to further publicize this RFI. All comments received were reviewed carefully by Institute staff and incorporated into the document, as appropriate.

The final version of the NIAMS Strategic Plan for FYs 2020-2024 was presented to the NIAMS Advisory Council at the Council's September 2019 meeting. After clearance to ensure compliance with the requirements described in the 21st Century Cure Act, the NIAMS Strategic Plan for FYs 2020-2024 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

During the development of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Strategic Plan for Fiscal Years (FYs) 2020-2024, the Institute issued two Requests for Information: the first to solicit initial comments on how the previous plan for FYs 2015-2019 should be modified to reflect progress over the past 5 years, and the second to invite public feedback on the draft NIAMS Strategic Plan for FYs 2020-2024.

Request for Information (RFI) on the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Strategic Plan for Fiscal Years (FYs) 2020-2024

Notice Number: NOT-AR-19-009

Key Dates
Release Date: September 14, 2018
Response Date: October 26, 2018

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 5 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:

- Research opportunities in the NIAMS Long-Range Plan for Fiscal Years (FY) 2015-2019 that should be modified because of progress over the past 5 years.
- Emerging research needs and opportunities that should be added to the plan.
- Cross-cutting scientific themes (e.g., pain, regenerative medicine) or research-related themes (e.g., innovation) common to all, or most, of the disease and tissue-specific topics (systemic rheumatic and autoimmune diseases, skin biology and diseases, bone biology and diseases, joint biology and diseases and orthopaedics, and muscle biology and diseases) within the NIAMS mission that should be included in the plan.

NIAMS also welcomes your general comments, including those regarding the extent to which the FYs 2015-2019 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 FYs 2015-2019 Plan that should be modified due to progress over the past 5 years, or a new opportunity for research not covered in the FYs 2015-2019 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 Submit a Response

Responses to this RFI must be submitted electronically at https://grants.nih.gov/grants/rfi/rfi.cfm?ID=81.

Responses must be received by October 26, 2018.

Responses to this RFI are voluntary. **Do not include any proprietary, classified, confidential, trade secret, or sensitive information in your response.** The responses will be reviewed by NIAMS staff, and individual feedback will not be provided to any responder. 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 submitted information on public NIH websites, in reports, in summaries of the state of the science, in any possible resultant solicitation(s), grant(s), or cooperative agreement(s), or in the development of future funding opportunity announcements.

This RFI is for information and planning purposes only and shall not be construed as a solicitation, grant, or cooperative agreement, or as an obligation on the part of the Federal Government, the NIH, or individual NIH Institutes and Centers to provide support for any ideas identified in response to it. The Government will not pay for the preparation of any information submitted or for the Government's use of such information. No basis for claims against the U.S. Government shall arise as a result of a response to this request for information or from the Government's use of such information.

We look forward to your input and hope that you will share this RFI document with your colleagues.

Inquiries
Please direct all inquiries to:

Cindy Caughman, M.P.H.
Chief, Science Policy and Planning Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Telephone: 301-496-8190
Email: niamslrpfeedback@mail.nih.gov

Request for Information (RFI) on the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Strategic Plan for Fiscal Years (FYs) 2020-2024

Notice Number: NOT-AR-19-010
Key Dates
Release Date: June 21, 2019
Response Date: July 12, 2019

Related Announcements
NOT-AR-19-009

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 Strategic Plan for Fiscal Years 2020-2024 to help guide the research it supports over the next 5 years. The Institute issued a previous Request for Information (NOT-AR-19-009) to solicit initial comments on how the previous plan for fiscal years 2015-2019 should be modified to reflect progress over the past 5 years. The Institute also gathered additional input through listening sessions with the community. Based on this feedback, along with input from the NIAMS Advisory Council and its Working Group for the Strategic Plan, the Institute has drafted the NIAMS Strategic Plan for FYs 2020–2024 (https://grants.nih.gov/grants/rfi/NIAMS-Strategic-Plan-2020-2024.pdf). We are now seeking input on this draft.

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 on the draft NIAMS Strategic Plan for FYs 2020-2024 (https://grants.nih.gov/grants/rfi/NIAMS-Strategic-Plan-2020-2024.pdf).

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 draft of the Strategic Plan will be presented at the September 2019 meeting of the NIAMS Advisory Council and posted on the NIAMS website when it is approved.

How to Respond

Responses to this RFI must be submitted electronically at http://grants.nih.gov/grants/rfi/rfi.cfm?ID=89.

Responses must be received by July 12, 2019.

Responses to this RFI are voluntary. **Do not include any proprietary, classified, confidential, trade secret, or sensitive information in your response.** The responses will be

reviewed by NIAMS staff, and individual feedback will not be provided to any responder. 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 submitted information on public NIH websites, in reports, in summaries of the state of the science, in any possible resultant solicitation(s), grant(s), or cooperative agreement(s), or in the development of future funding opportunity announcements.

This RFI is for information and planning purposes only and shall not be construed as a solicitation, grant, or cooperative agreement, or as an obligation on the part of the Federal Government, the NIH, or individual NIH Institutes and Centers to provide support for any ideas identified in response to it. The Government will not pay for the preparation of any information submitted or for the Government's use of such information. No basis for claims against the U.S. Government shall arise as a result of a response to this request for information or from the Government's use of such information.

We look forward to your input and hope that you will share this RFI document with your colleagues.

Inquiries
Please direct all inquiries to:

Cindy Caughman, M.P.H.
Chief, Scientific Planning, Policy, and Analysis Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Telephone: 301-496-8271
Email: niamslrpfeedback@mail.nih.gov

Appendix 3: Development Timeline for the NIAMS Strategic Plan for Fiscal Years 2020-2024

2018	September	Update to NIAMS Advisory Council on the development of the plan.
	September/ October	Request for Information posted in the *NIH Guide for Grants and Contracts* and on the NIAMS website for public input on research opportunities that should be modified because of progress over the past 5 years, emerging research needs and opportunities that should be added to the plan, and cross-cutting scientific themes or research-related themes common to all, or most, of the disease- and tissue-specific topics within the NIAMS mission that should be included in the plan.
	November/ December	Listening sessions held as teleconferences for: • systemic rheumatic and autoimmune diseases • skin biology and diseases • muscle biology and diseases • bone biology and diseases • joint biology, diseases, and orthopaedics • NIAMS Coalition Listening session for training and health disparities with participants who attended the NIAMS Forum for Clinical Mentored K Awardees
2019	February	• Update to NIAMS Advisory Council on the development of the plan. • NIAMS Advisory Council Working Group for the Strategic Plan convened.
	May	Draft plan presented to the NIAMS Advisory Council and its Working Group for the Strategic Plan for review and input.
	June/July	• Report and recommendations from the Working Group presented to NIAMS Advisory Council for discussion. • 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.