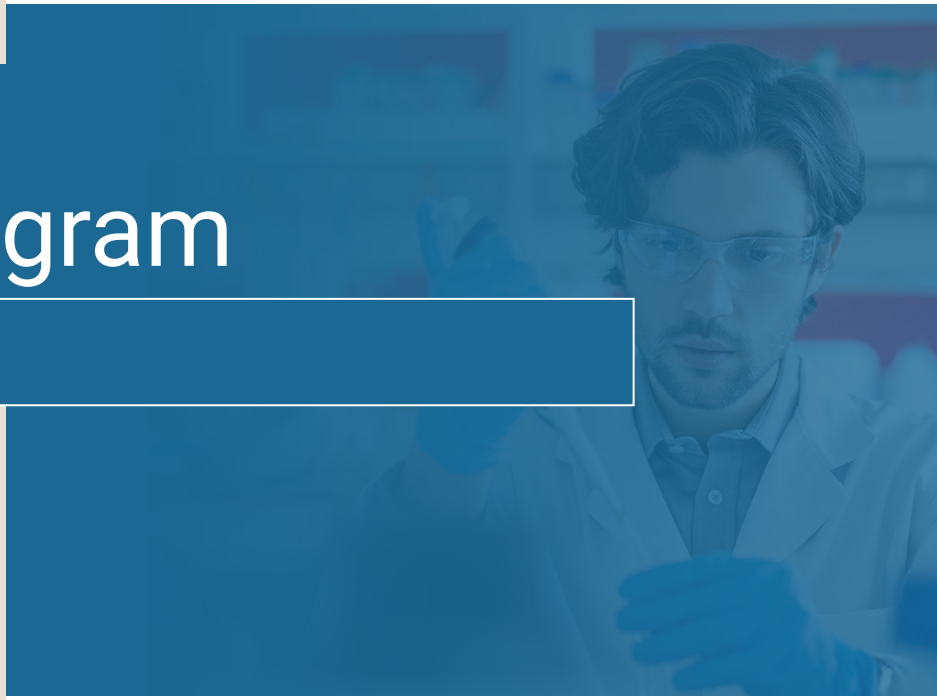
CDMRP
Department of Defense

Scleroderma Research Program

Strategic Plan



INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. Programs managed by the CDMRP have formalized strategic plans that identify program-specific research priorities, how to best address these urgencies, short- and long-term goals, investment strategies, and ways to identify and evaluate program successes with respect to the priorities.

This document presents the current strategy for the CDMRP's Scleroderma Research Program (SRP). The SRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the SRP is congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The SRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

SRP BACKGROUND AND OVERVIEW

Scleroderma research was funded by the CDMRP for 10 years as a congressionally directed topic under the Peer Reviewed Medical Research Program (PRMRP). During the fiscal years that scleroderma was a topic area within the PRMRP (fiscal year 2008 [FY08], FY10–FY13, and FY15–FY18), 26 awards were funded with a topic-specific investment of $23.21 million (M). The PRMRP scleroderma investment is shown in **Figure 1**. Approximately 77% of the scleroderma research funded by the PRMRP was invested in understanding the cell biology, pathobiology, and detection and diagnosis of scleroderma.

In FY20, Congress directed $5M to scleroderma research in the Defense Appropriations Act, thus establishing the SRP to support innovative research toward decreasing the impact of scleroderma on Service Members, Veterans, and the American public. In its inaugural year, the SRP funded 5 awards totaling $4.43M. The SRP investment is shown in **Figure 2**. The FY21 Defense Appropriation Act provided an additional $5M to the SRP. The overarching vision and mission of the SRP are as follows:

VISION: To combat scleroderma through a partnership of scientists, clinicians, and consumers

MISSION: To fund and facilitate the most promising, highest quality research aimed at understanding mechanisms, improving therapies, and ultimately curing scleroderma for Service Members, Veterans, and the American public

Scleroderma, also called systemic sclerosis (SSc), is a poorly understood heterogeneous rare autoimmune disease resulting from an overproduction of the protein collagen. This leads to thickening of the skin, vasculopathy, autoimmunity, inflammation, and fibrosis. Because the immune system is affected by scleroderma, symptoms often resemble those of other autoimmune diseases, making diagnosis and treatment difficult. Many patients suffer for years before receiving a correct diagnosis.

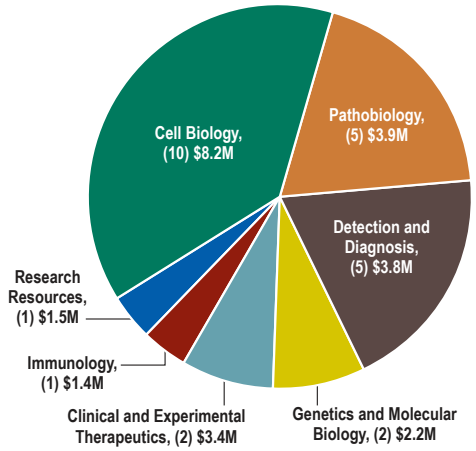


Figure 1. FY08–FY19 PRMRP Scleroderma Awards by Scientific Classification Code in Millions
(Number of Awards in Parentheses)

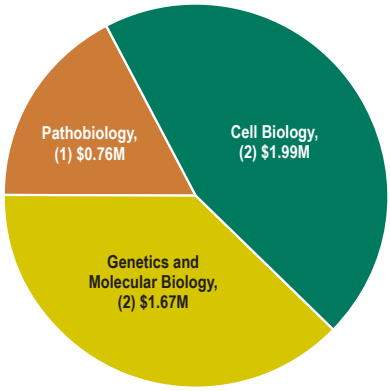


Figure 2. FY20 SRP Awards by Scientific Classification Code in Millions
(Number of Awards in Parentheses)

The prevalence of scleroderma is about 250 per million, and the incidence is about 20 per million adults,[1] with approximately 70,000 scleroderma cases in the United States. Although scleroderma affects individuals of all ages, including children, incidence is most likely between the ages of 40–60, with females four times more likely to develop scleroderma than males. Scleroderma has the highest mortality rate of any systemic autoimmune disease, with interstitial lung disease as the leading cause of scleroderma-related mortality. Due to the lack of validated biomarkers or effective disease-modifying therapeutics for scleroderma, better treatment options are a critical need for scleroderma patients.

RESEARCH FUNDING LANDSCAPE

Funding for SRP research comes from many sources through a variety of programs. Many researchers have received federal funding through the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). To maximize the SRP's ability to fill gaps and leverage with other efforts in the scleroderma research community, it is important for the program to consider the focus and successes of other major funding organizations of scleroderma-related research. A comparison of scleroderma-invested research across federal and non-federal organizations is shown in **Figure 3**.

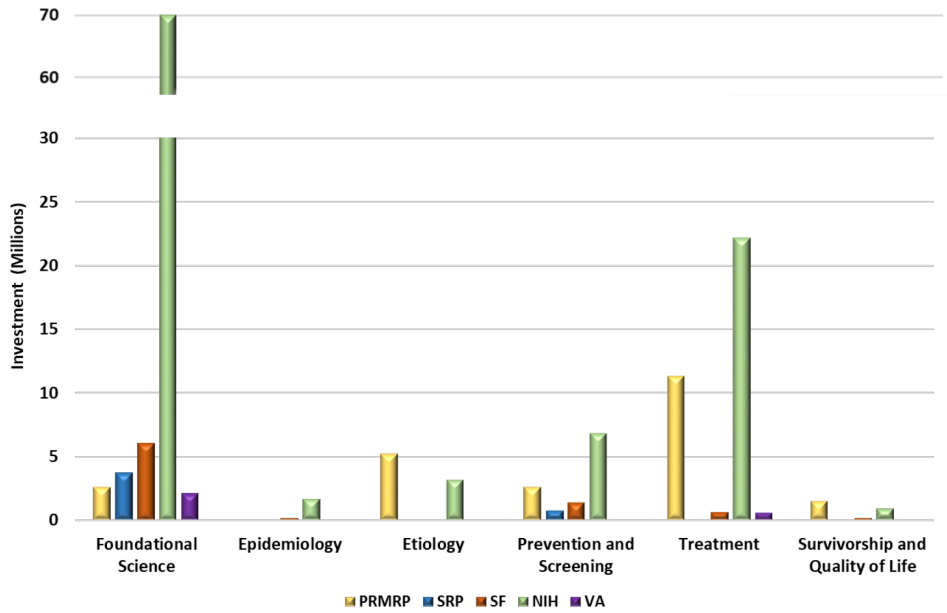


Figure 3. Federal and Non-Federal Investment in Scleroderma Research

STRATEGIC DIRECTION

To ensure that each program's research portfolio reflects not only the most meritorious science, but also the most programmatically relevant research, the CDMRP utilizes a two-step review procedure for research applications that is composed of a scientific peer review and a separate programmatic review. The scientific peer review is conducted by an external panel that is recruited specifically for each peer review session. Peer review involves the expertise of scientists, clinicians, military members, and consumers (patient advocates). Each application is judged on its own scientific and technical merit with respect to the described criteria in the funding opportunity solicitation. The second tier of review, programmatic review, includes discussions by experts in the field, such as the Programmatic Panel for the SRP. These experts, which include scientists, clinicians, consumers, and members of the military, assess the applications based on the scientific peer review ratings and summaries, portfolio balance, programmatic intent, and scientific merit. The SRP Programmatic Panel (*https://cdmrp.army.mil/srp/panels/panels21*) has representation from leading federal scleroderma funding agencies such as the VA and the National Institute of Arthritis and Musculoskeletal and Skin Diseases as well as non-federal consumer-focused advocacy groups, which fund a smaller portion of scleroderma research. The Programmatic Panel members provide scleroderma expertise as well as knowledge of their organizations' research and funding efforts, enabling the SRP to work synergistically within the scleroderma community while avoiding duplication of effort.

During the FY21 Vision Setting meeting, nine *Research Areas of Emphasis* were identified to address the SRP's five *Overarching Challenges*:

Overarching Challenges:

Understanding Cell Biology

Understanding Disease Heterogeneity

Identifying Therapeutic Targets

Conducting Clinical Trials

Addressing Quality of Life and Survivorship

Research Areas of Emphasis:

1. Define biomarkers ('omics and/or molecular markers, cell subsets, imaging, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life.
2. Utilize systems biology, multi-omics and/or preclinical screening approaches (including but not limited to high-throughput screens, the development of animal models, three-dimensional [3D] tissue culture and/or organoids) with the intent to develop drug testing models in order to understand the heterogeneity of disease as well as to develop prevention and therapeutic interventions.
3. Conduct studies of diverse populations to include the development of cohorts and identification of potential measures of patient outcomes to understand the unique burden of the disease.
4. Define the functional role of epigenetic changes, multiple cell types, and molecules that mediate pathogenesis and/or initiate or propagate organ-specific disease activity using preclinical models and clinical samples.
5. Develop and validate short- and long-term organ-specific and composite clinical outcomes measures to determine treatment efficacy:
    - Develop better quantifiable and reproducible measures to assess clinical manifestations including skin, heart, Raynaud phenomenon, calcinosis cutis, or gastrointestinal tract morbidity in scleroderma.
    - Validate patient-reported outcome measurements to aid in the approval of drug and therapies.
    - Develop and validate intermediate biological/surrogate endpoints to support larger clinical proof-of-concept/proof-of-mechanism trials.
6. Conduct population-based or cohort studies to understand the prevalence, heterogeneity, and course of this disease, its manifestations, and its impact on health outcomes and activities for daily living:
    - Understand the unique burden of disease in disease in diverse populations.
    - Understand disease heterogeneity (course of disease, prevalence, and associated factors).
    - Utilize disease registries linked to biological samples and high-quality clinical data and patient-reported outcomes.
    - Conduct fine phenotyping of clinical subsets to address heterogeneity.

7. Understand and improve the impact of disease and its treatment on the patient's experience and quality of life:
    - Develop interventions to improve coping with disease.
    - Identify main concerns of patients to inform development and validation of patient-reported outcomes.
    - Understand the link between molecular, laboratory, and clinical measures and the patient's quality of life.
8. Development of clinical trial platforms that enable rapid comparison of different therapeutic approaches on a pilot basis.
9. Conduct secondary analysis of scleroderma and other similar disease datasets to identify novel targets and biomarkers that can be validated in existing or new models.

Figure 4: Research Areas of Emphasis Aligned to the Overarching Challenges

Overarching Challenges	Research Areas of Emphasis
Understanding Cell Biology	• Define functional role of epigenetic changes, multiple cell types, and molecules that mediate pathogenesis and/or initiate or propagate organ-specific disease activity using preclinical models and clinical samples. • Define biomarkers ('omics and/or molecular markers, cell subsets, imaging, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life
Understanding Disease Heterogeneity	• Conduct population-based or cohort studies to understand the prevalence, heterogeneity, and course of this disease, its manifestations, and its impact on health outcomes and activities for daily living: - Understand the unique burden of disease in disease in diverse populations. - Understand disease heterogeneity (course of disease, prevalence, and associated factors). - Utilize disease registries linked to biological samples and high-quality clinical data and patient-reported outcomes. - Conduct fine phenotyping of clinical subsets to address heterogeneity. • Conduct studies of diverse populations to include the development of cohorts and identification of potential measures of patient outcomes to understand the unique burden of disease. • Define functional role of epigenetic changes, multiple cell types, and molecules that mediate pathogenesis and/or initiate or propagate organ-specific disease activity using preclinical models and clinical samples.
Identifying Therapeutic Targets	• Utilize systems biology, multi-omics and/or preclinical screening approaches (including but not limited to high-throughput screens, the development of animal models, three-dimensional [3D] tissue culture and/or organoids) with the intent to develop drug testing models in order to understand the heterogeneity of disease as well as to develop prevention and therapeutic interventions. • Define biomarkers ('omics and/or molecular markers, cell subsets, imaging, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life. • Develop and validate short- and long-term organ-specific and composite clinical outcomes measures to determine treatment efficacy: - Develop better quantifiable and reproducible measures to assess clinical manifestations including skin, heart, Raynaud phenomenon, calcinosis cutis, or gastrointestinal tract morbidity in scleroderma. - Validate patient-reported outcome measurements to aid in the approval of drug and therapies. - Develop and validate intermediate biological/surrogate endpoints to support larger clinical proof-of-concept/proof-of-mechanism trials. • Conduct secondary analysis of scleroderma and other similar disease datasets to identify novel targets and biomarkers that can be validated in existing or new models.
Conducting Clinical Studies/Trials	• Develop and validate short- and long-term organ-specific and composite clinical outcomes measures to determine treatment efficacy: - Develop better quantifiable and reproducible measures to assess clinical manifestations including skin, heart, Raynaud phenomenon, calcinosis cutis, or gastrointestinal tract morbidity in scleroderma. - Validate patient-reported outcome measurements to aid in the approval of drug and therapies. - Develop and validate intermediate biological/surrogate endpoints to support larger clinical proof-of-concept/proof-of-mechanism trials. • Conduct population-based or cohort studies to understand the prevalence, heterogeneity, and course of this disease, its manifestations, and its impact on health outcomes and activities for daily living: - Understand the unique burden of disease in disease in diverse populations. - Understand disease heterogeneity (course of disease, prevalence, and associated factors). - Utilize disease registries linked to biological samples and high-quality clinical data and patient-reported outcomes. - Conduct fine phenotyping of clinical subsets to address heterogeneity. • Conduct studies of diverse populations to include the development of cohorts and identification of potential measures of patient outcomes to understand the unique burden of disease. • Develop clinical trial platforms that enable for rapid comparison of different therapeutic approaches on a pilot basis.

Overarching Challenges	Research Areas of Emphasis
Addressing Quality of Life and Survivorship	• Understand and improve the impact of disease and its treatment on the patient's experience and quality of life: - Develop interventions to improve coping with disease. - Identify main concerns of patients to inform development and validation of patient-reported outcomes. - Understand the link between molecular, laboratory, and clinical measures and the patient's quality of life. • Define biomarkers ('omics and/or molecular markers, cell subsets, imaging, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life. • Conduct studies of diverse populations to include the development of cohorts and identification of potential measures of patient outcomes to understand the unique burden of disease. • Conduct population-based or cohort studies to understand the prevalence, heterogeneity, and course of this disease, its manifestations, and its impact on health outcomes and activities for daily living: - Understand the unique burden of disease in disease in diverse populations. - Understand disease heterogeneity (course of disease, prevalence, and associated factors). - Utilize disease registries linked to biological samples and high-quality clinical data and patient-reported outcomes. - Conduct fine phenotyping of clinical subsets to address heterogeneity.

FY21 INVESTMENT STRATEGY

To achieve the strategic goals identified above, the SRP will focus its investment on translational and paradigm-shifting research that has the potential to make a significant advancement in the scleroderma research field. The Idea Development Award and Translational Research Partnership Award mechanisms are summarized below.

- Idea Development Award
  - Provides funding for ideas that are in the early stages of development and have the potential to yield high-impact findings and new avenues of investigation.
  - Emphasis is on conceptually high-risk, high-reward studies that could lead to critical discoveries or major advancements in scleroderma research and/or improvements in patient care.
  - Encourages applications in which an established scleroderma researcher partners with a new investigator in the early stages of their career.
- Translational Research Partnership Award
  - Supports partnerships between clinicians, research scientists, and/or other disciplines that will accelerate the movement of promising ideas in scleroderma into clinical application. Emphasis is on translational research collaborations between two or more investigators (up to three) to address a central problem or question in scleroderma in a manner that would be less readily achievable through separate efforts. One partner in the collaboration must be a clinician (M.D., D.O. or equivalent) with clinical duties and/or responsibilities, and one partner must have experience in scleroderma research as demonstrated by active funding and/or recent publications.

Taking into account available congressional appropriations for each fiscal year, this investment strategy will be re-evaluated and updated as necessary during the program's annual Vision Setting meeting.

MEASURING PROGRESS

The SRP will measure its success in the near term based on successful investments in the SRP's Focus Areas. Long-term success will be evaluated based on contributions to the scientific community, follow-up research linked to SRP funding, and research linked to alternations in clinical treatments and interventions that have a direct impact on patient outcomes and/or quality of life.

MEASURES OF SUCCESS

- Number of applications received and funded within each of the SRP Focus Areas
- Completion of research aims for funded research
- Contribution to the scientific community (publications, presentations, patents, etc.)
- Subsequent federal or non-federal funding of initial SRP-funded research
- Alternations in clinical treatment paradigms resulting from SRP-funded research
- Investigational New Drug Application/Investigative New Device applications to the Food and Drug Administration as a result of SRP-funded research.

REFERENCES

1. *https://sclerodermainfo.org/prevalence-and-incidence-of-systemic-scleroderma-in-the-us/.*