



# 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. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP’s two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,<sup>1</sup> the committee recommended that each CDMRP program “... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future,” and that these strategic plans “should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives.”

In response to these recommendations, 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.

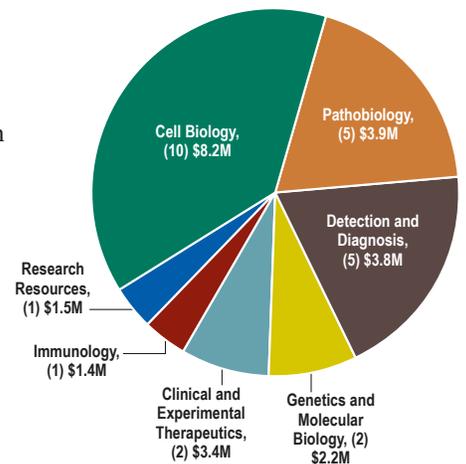
### SRP BACKGROUND AND OVERVIEW

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 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 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. 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 improved therapies, and ultimately, a cure for scleroderma for Service members, Veterans, and the American public



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



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.

The prevalence of scleroderma is about 250 per million, and the incidence is about 20 per million adults,<sup>2</sup> 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 being 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

In FY20, the CDMRP released a request for information (RFI) to PRMRP-funded scleroderma investigators, researchers funded by other government agencies and foundations, and scleroderma advocates. The RFI asked survey respondents to address the most critical needs in scleroderma research. The results of the RFI, compiled from over 60 responses, were used to inform stakeholders of funding gaps, challenges facing the scleroderma community, and elucidate potential research priorities for the treatment of scleroderma. (see Stakeholders Meeting below).

Funding for SRP research comes from many sources through a variety of programs. Many researchers have received federal funding through the NIH and the 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 the successes of other major funding organizations of scleroderma-related research.

## STAKEHOLDERS MEETING

The CDMRP hosted the inaugural SRP Stakeholders meeting on April 29, 2020. The SRP Stakeholders meeting brought together representatives from scleroderma non-profit organizations, academia, and Government institutions. This diverse group of 40 individuals shared perspectives on which initiatives have the greatest potential to propel the science forward, break down potential barriers in research and patient outcomes, address key knowledge or scientific gaps, and identify potential approaches for the treatment of scleroderma. The information gathered through the Stakeholders meeting was published on the SRP website (<https://cdmrp.army.mil/srp/pdf/SRP%20FY20%20StakeHolders%20Summary.pdf>) and was used to inform the FY20 SRP of the state of the science ahead of the FY20 Vision Setting meeting. The SRP Stakeholders Meeting participants identified the following areas of emphasis, which were used at the FY20 Vision Setting meeting held May 21, 2020.

Research Continuum	Research Gaps	Research Priorities (Areas of Emphasis)
<b>Foundational Science:</b> Basic discovery science	The molecular mechanisms and pathogenesis of scleroderma are poorly understood and there is a need to identify novel and/or innovative therapeutic targets.	<ul style="list-style-type: none"> <li>Understand the strong female sex bias in scleroderma and why males have more severe disease.</li> <li>Understand the different biological/metabolic pathways that differentiate subsets of patients (genetic, clinical phenotype, race/ethnicity).</li> </ul>
<b>Epidemiology:</b> Population-level (to include at-risk) descriptive and characterization in nature; the study of the distribution of associations between health-related states	Population-based or cohort studies are needed to understand the prevalence, heterogeneity and course of this disease, its manifestations and its impact on health outcomes and activities for daily living.	<ul style="list-style-type: none"> <li>Expansion of early disease registries linked to biological samples and high-quality clinical data and patient reported outcomes.</li> <li>Direct patient recruitment: Enroll patient partners through Facebook or other platforms to avoid referral bias at tertiary centers.</li> <li>Investigate fine phenotyping of clinical subsets to address heterogeneity.</li> </ul>
<b>Etiology:</b> Neurobiological mechanisms of the disease to include possible causes of disorder.	Scleroderma has the highest mortality rate of any systemic autoimmune disease and further research is critical to decrease organ involvement, especially in the lungs.	<ul style="list-style-type: none"> <li>Understand the functional implications of epigenetic changes in scleroderma and the role of epigenetic changes in disease development.</li> <li>Define the target cells of the autoimmune response that initiate and/or propagate organ-specific disease activity.</li> <li>Develop models that are more suitable to study the disease or closely mimic the disease.</li> </ul>



Research Continuum	Research Gaps	Research Priorities (Areas of Emphasis)
<p><b>Prevention and screening:</b> Population, indicated prevention/ intervention at different stages of illness; screening measures; assessment tools and measurement; training</p>	<p>There is a need for validated biomarkers and other approaches for early diagnoses, monitoring disease progression and its associated complications, assessment of treatment response to prevent, arrest, or reverse the symptoms of scleroderma.</p>	<ul style="list-style-type: none"> <li>Define biomarkers ('omics, and or molecular markers, cell subsets, imaging, and patient reported outcomes) that help inform choice of therapeutics or predict course of treatment response of lung fibrosis, pulmonary, vascular disease, cardiac, and renal in patients with early disease.</li> <li>Define biomarkers that help inform choice of therapeutics (immunosuppressive/ anti-fibrotic) or predict course or treatment response of ulcers, gastrointestinal, or severe skin disease (morbidity)</li> <li>Develop cohorts from diverse populations to validate potential biomarkers.</li> </ul>
<p><b>Treatment:</b> Aimed at symptom amelioration at different stages of illness including refractory, chronic, relapse, relapse prevention; address comorbidities; follow-up</p>	<p>There are very few therapies that are modestly effective for certain manifestations of scleroderma; these have considerable risks and adverse effects that limit their usefulness. There is a critical need for novel and/or innovative therapies and re-purposing of existing therapies.</p>	<ul style="list-style-type: none"> <li>Develop and design innovative clinical trials.</li> <li>Develop and validate organ specific and composite outcomes measures that help identify what treatments are actually working.</li> <li>Utilize clinical and molecular/laboratory measures to define homogeneous groups or relevant subsets of patient(s) to determine treatment and response - personalize medicine.</li> </ul>
<p><b>Survivorship/quality of life:</b> Focused on system of care improvements and provider and non-healthcare provider.</p>	<p>Research is needed to understand and improve the impact of the disease and its treatment on the patient's experience and quality of life. Research is also needed to develop interventions to improve coping with the disease.</p>	<ul style="list-style-type: none"> <li>Identify main concerns of patients to inform development and validation of patient-reported outcomes.</li> <li>Develop interventions that improve the quality of life.</li> <li>Understand the link between what we see in terms of molecular, laboratory, and clinical measures and the patient's quality of life.</li> </ul>

**SRP PROGRAMMATIC PANEL**

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/panels20>) 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.

**STRATEGIC DIRECTION**

During the inaugural Vision Setting meeting, the SRP Programmatic Panel used the Scleroderma Research Continuum (Figure 2) to identify the needs of the scleroderma community and develop a course forward for research in scleroderma. The Scleroderma Research Continuum represents a research framework within which studies are organized along a progression that includes six topic areas: foundational science, epidemiology, etiology, prevention and screening, treatment, and survivorship and quality of life.

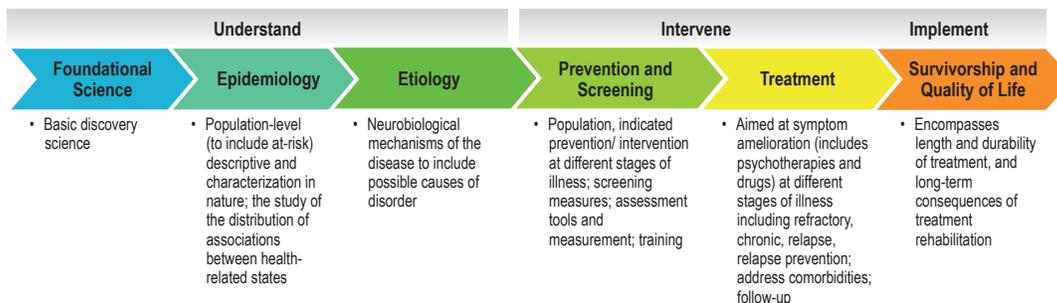


Figure 2. Scleroderma Research Continuum



## NEAR-TERM FOCUS – FY20 FOCUS AREAS

Using the Scleroderma Research Continuum, the SRP has identified seven Focus Areas covering foundation science, etiology, prevention and screening, and treatment for FY20. The SRP Focus Areas will be re-evaluated each fiscal year.

- Development of clinical trial platforms that enable for rapid comparison of different therapeutic approaches on a pilot basis.
- Defining 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.
- Secondary analysis of scleroderma, and other similar disease datasets, to identify novel targets and biomarkers that can be validated in existing or new models.
- Understanding the different biological/metabolic pathways that differentiate subsets of patients (gender, age, genetic, clinical phenotype, race/ethnicity).
- Utilizing systems biology, multi-omics and pre-clinical screening approaches to understand the heterogeneity of disease, prevention and therapeutics inventions.
- Development of cohorts from diverse populations (longitudinal) to validate potential biomarkers (i.e., replication studies).
- Defining epigenetic changes, multiple cell types and molecules that mediate pathogenesis.

## MEDIUM- TO LONG-TERM FOCUS

Over the long term, the SRP will consider expanding its focus to include patient-centric clinical trials aimed at symptom amelioration at different stages of illness including refractory, chronic, relapse, and relapse prevention. Long-term focus will be in the areas of epidemiology, disease prevalence in minorities, and survivorship/quality. The SRP expects the medium- to long-term priorities to evolve based on research funded in the near term and progress made by others in the field.

- 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 minorities.
  - Understand disease heterogeneity (prevalence and associated factors).
  - Expand early disease registries linked to biological samples and high-quality clinical data and patient reported outcomes.
  - Conduct fine phenotyping of clinical subsets to address heterogeneity.
- Understand and improve the impact of the disease and its treatment on the patient’s experience and quality of life.
  - Develop interventions to improve coping with the disease.
  - Identify main concerns of patients to inform development and validation of patient-reported outcomes.
  - Identify interventions that improve quality of life.
  - Understand the link between molecular, laboratory and clinical measures and the patient’s quality of life.
- Define cells that initiate or propagate organ-specific disease activity.
- Define epigenetic changes, multiple cell types and molecules that mediate pathogenesis.
  - Understand the functional implications of epigenetic changes in scleroderma.
  - Define the target cells of the autoimmune response that initiate and/or propagate organ-specific disease activity.
  - Develop models, such as organoid structures, that are more suitable to model the disease or closely mimic the disease.
- Develop and validate short- and long-term organ-specific and composite clinical outcomes measures to determine treatment efficacy.
  - Develop better clinical and biomarker measures to measure, heart, Raynaud phenomenon, calcinosis cutis, and gastrointestinal tract morbidity in scleroderma.
- Develop and validate intermediate biologic/surrogate endpoints to support larger clinical proof of concept/proof of mechanism trials



## FY20 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 and research scientists that will accelerate the movement of promising ideas in scleroderma into clinical applications. Emphasis is on translational research collaborations between two or more investigators 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 research scientist and another must be a clinician. In addition, one partner in the collaboration must be a new investigator in the early stages of their career.

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 on contributions to the scientific community, follow-up research linked to SRP funding, and research that is 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 FDA as a result of SRP funded research.

## REFERENCES

1. Evaluation of the Congressionally Directed Medical Research Programs Review Process. 2016. The National Academies of Sciences, Engineering, and Medicine. The National Academies Press. Washington, DC.
2. <https://sclerodermainfo.org/prevalence-and-incidence-of-systemic-scleroderma-in-the-us/>