CDMRP
Department of Defense

Spinal Cord Injury 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,[1] 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 Spinal Cord Injury Research Program (SCIRP). The SCIRP Strategic Plan identifies the high-impact research goals that are 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 SCIRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The SCIRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

SCIRP BACKGROUND AND OVERVIEW

Congress established the SCIRP in fiscal year 2009 (FY09), prompted by recognition of spinal cord injury (SCI) as one of the many serious wounds resulting from conflicts in Iraq and Afghanistan that require multiple levels of research and treatment. The original Congressional language noted that research into repairing/regenerating damaged spinal cords (SCs) and improving rehabilitative therapies offers real promise for enhancing the long-term care of wounded Soldiers.

Following the initial FY09 SCIRP appropriation, input was gathered through a request for information and an in-person meeting in March 2009 with stakeholders from academia, the military Services, the VA, the NIH, other federal agencies, industry, and SCI advocacy organizations. The report from this meeting informed the first SCIRP Vision Setting meeting in May 2009. The first Program Announcements encouraged proposals targeting traumatic SCI and specifically addressing the critical needs of the SCI community in the areas of neuro-protection and repair, rehabilitation and the complications of chronic SCI, and outcome measures.

The Focus Areas and award mechanisms offered by the program have been revisited at annual Vision Setting meetings and have evolved to emphasize translational and clinical research along the continuum of care, from management of the acute injury through rehabilitation to health and quality of life issues for individuals living with SCI.

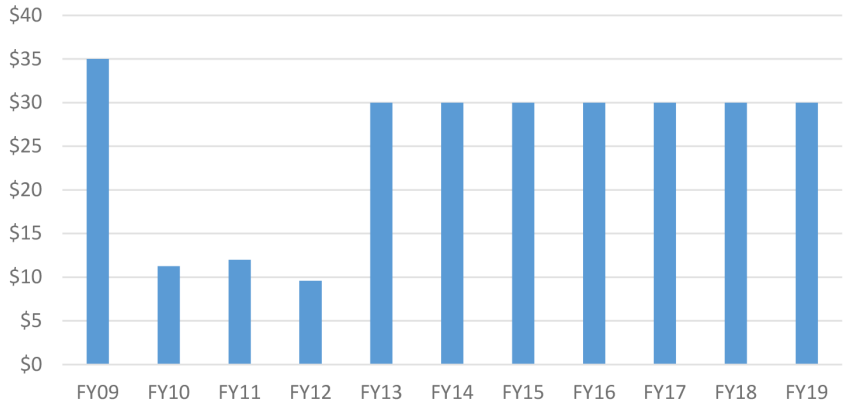
VISION: Advance the treatment and management of spinal cord injury and ameliorate its consequences relevant to injured Service members

MISSION: To fund research and encourage multidisciplinary collaborations for the development and translation of more effective strategies to improve the health and well-being of Service members, Veterans, and other individuals with spinal cord injury

FUNDING HISTORY

The initial FY09 Congressional appropriation for a competitive, peer-reviewed SCI research and treatment program was $35 million (M). The total appropriation from FY09-FY18 was $247.85M, and the FY19 appropriation is $30M.

Figure 1: SCIRP Annual Congressional Appropriation (Millions of dollars)

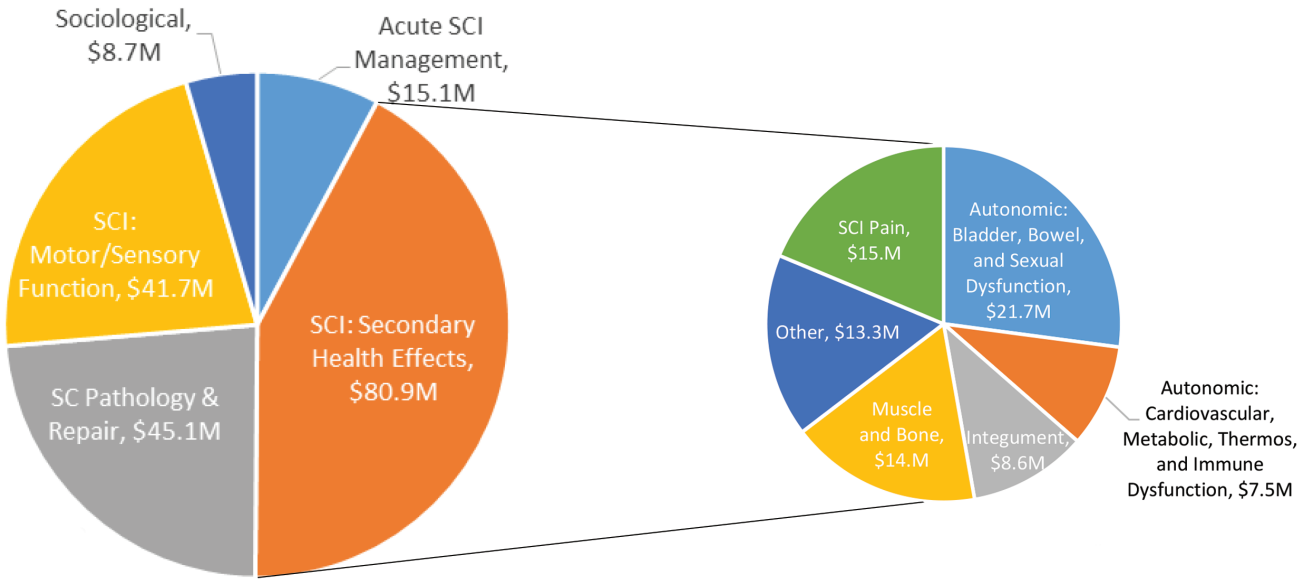


RESEARCH PORTFOLIO

Between FY09 and FY17, the SCIRP funded 219 awards in traumatic SCI research. The program supports basic research in SCI where, for example, underlying mechanisms such as the development of neuropathic pain are still not understood. However the program focuses on translational (41% of the investment by $) and clinical (47%) research, in keeping with the mission of developing and translating effective strategies to improve the health and well-being of individuals with SCI.

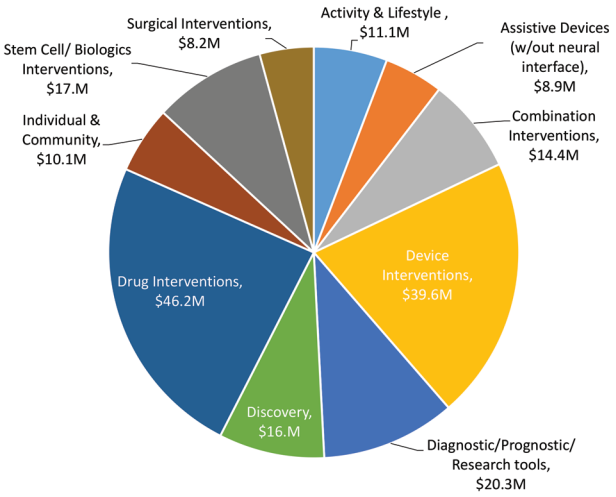
Based on a review of the state of the science at annual Vision Setting meetings, the SCIRP continues to address systems or problems across the continuum of care. Figure 2 shows that the SCIRP has support for early care, including acute SCI management and SC pathology and repair, as well as SCI motor/sensory function and SCI secondary health effects. Early care, including neuroprotective interventions that could be initiated at the point of injury, are particularly relevant to military considerations of injury care in far-forward environments. Figure 2 also breaks down the investment in secondary health effects of SCI, showing that nearly half of the program investment is in bladder and bowel dysfunction and neuropathic pain, in keeping with the importance of these issues for all individuals with SCI.

Figure 2: SCIRP Funded Research FY09-FY17



SCI is a multifaceted neurotrauma, and the SCIRP is making progress toward improving healthcare for individuals with SCI through a range of approaches, as shown in Figure 3. Currently, the largest investments are in device and drug interventions. The program also supports research in development of diagnostic and prognostic tools. A new category added in 2018 is tracking investment in combination interventions, i.e., combining approaches, often activity and lifestyle with a device or drug, to maximize function. The program anticipates that this area will grow in the coming years as clinical science moves toward personalized treatment approaches to maximize outcomes for individuals with SCI.

Figure 3: Interventions for SCI



RESEARCH ACCOMPLISHMENTS

Outcomes achieved or in process for the SCIRP include 252 publications, 16 patents (applied for or issued), and 36 clinical trials. Award data and abstracts of funded research proposals can be viewed on the CDMRP website (http://cdmrp.army.mil). Some highlights from SCIRP-funded research include the following:

- Translational research using large animal models to map causal relationships between intensive care management of cardiovascular functions after SCI and later neurological outcomes to inform clinical practice guidelines.
- Using near-infrared spectroscopy as a real-time measurement tool for monitoring SC hemodynamics and oxygenation to guide clinical care of acute SCI. This information will guide management of acute SCI and has the potential to improve outcomes after injury.
- A multisite clinical trial (NCT02878850) assessing the efficacy and safety of early blood pressure manipulation in acute SCI injury.
- A knowledge network of acute SCI management that analyzes clinical variables, outcomes, and biomarkers to facilitate diagnosis, prognosis, and data-sharing (Transforming Research and Clinical Knowledge in Spinal Cord Injury or TRACK-SCI).
- Preclinical research supporting a successful Food and Drug Administration (FDA) application for ongoing clinical trials of stem cells in SCI (NCT01739023 and NCT02354625, supported through other funding)
- A study of stem cells in non-human primates, as recently reported in *Nature Medicine*,[2] that is part of a longer-term effort to develop a stem cell therapy for human testing.
- Acute Intermittent Hypoxia (AIH) appears to activate plasticity in spared neurons after injury and improve motor and other functions. The SCIRP is funding both translational studies to understand the mechanism of AIH and an early-stage clinical trial (NCT02632422) to evaluate AIH for improving overland walking after injury.
- A study in rats after SCI showed that daily stretching—modeled on the physical therapy given to patients with SCI in acute or chronic phases of SCI—may actually reduce motor function. A follow-up study is in progress that could lead to changes in clinical care.
- Development of an implantable neuroprosthetic device to normalize bladder function after SCI. A wireless device for control of bladder incontinence and voiding was developed and tested in rats with SCIRP funding. Further work is currently being continued with other Department of Defense (DoD) funding, and the project anticipates having a product for human testing in 2020.
- A study developing a new culturally appropriate instrument for assessing the burdens and benefits to caregivers for Veterans with SCIs.

RESEARCH AND FUNDING ENVIRONMENT

STATE OF THE SCIENCE

SCI is a serious issue within the military Services and for the American public. There were approximately 6,000 cases of traumatic SCI in the military Services reported from 2000-2009.[3] An estimated 17,700 new SCIs occur every year in the United States, with a reported 288,000 U.S. persons living with an SCI (based on data gathered through 2017 by the National Spinal Cord Injury Database[4]). The VA treats more than 27,000 Veterans with SCI and related disorders (SCI fact sheet published 2017[5]). An SCI leads

to impairment or loss of functions controlled by the SC below the level of injury. Average cost of care can range from $1M for the first year after injury for someone with a high injury resulting in tetraplegia to $537,271 for a person with a lower level of injury resulting in paraplegia,[4] with an average of $71,172-$191,436 for each year after for the life of the individual. In addition to loss of sensation and motor control, bladder and bowel dysfunction and neuropathic pain are frequent and serious consequences of SCI,[6] and persons with an SCI have increased mortality rates for infection, respiratory dysfunction, and cardiovascular, pulmonary, and urinary disease.[4] There are currently no treatments to fully repair or regenerate injured SCs.

Considering the continuum of care in SCI, research can be divided into three areas:

1. **Early and acute care**

   Optimal management of acute SCI has the goal of keeping the scope of damage to the SC as small as possible to reduce the loss of functional connections. Approaches include optimized surgical guidelines and intensive care control of cardiovascular functions to maintain optimal intra-cord perfusion and function. Evidence of the potential for optimized acute care to reduce loss of function comes from several clinical efforts, such as the STASCIS trial,[7] which showed the benefits of early decompression surgery in terms of neurological improvement. However, while management of cardiovascular function, blood pressure, and SC tissue perfusion could have significant impact on progression of the SCI, more information is needed on how to manage these variables for optimal neurological function outcomes. Challenges in this area include lack of detailed patient studies correlating outcomes with intensive care received and the difficulty of measuring perfusion functions within the injured SC.

   In addition to the immediate injury, SCI sets off a cascade of events continuing over hours and days after the initial trauma. These events include biochemical and cellular changes that can damage nerve cells and increase loss of function. Drug interventions that could block some of these damaging events include treatments to manage neuroinflammation and reduce oxidative stress. However, there is currently no consensus on what treatments clearly enhance recovery after SCI. Challenges in this area include determining which events in the injury cascade to target and poor translation of promising preclinical results to human therapy.

   A challenge of high relevance to the military is how to offer the best SCI care in far-forward and austere environments by developing acute injury management and neuroprotective interventions that can be deployed outside of a tertiary care hospital setting.

2. **Rehabilitation and restoration of function after SCI**

   Exercise and other functional training have shown that there is significant potential for plasticity and a regain of function in the residual SC. Training, including exoskeleton and other weight-supporting approaches, improves mobility and health. Neuroprosthetic devices, including epidural stimulation, are providing avenues to recruit functions in the SC below the injury and to activate the residual cord and retrain surviving neurons to provide new functionality. In parallel, therapies are being developed to induce greater neuroplasticity in the injured cord. Finally, research is still going forward in developing stem cell interventions to both promote the function of the residual cord and regrow connections across the site of injury.

   Although many opportunities exist in this area, there are also many challenges. Mechanisms of action of some of these promising interventions are still unknown. Dosing protocols for functional training and best combinations of functional and neuroplasticity interventions need to be clarified, which will include determining how to provide individuals with the best combination of treatments based on their specific injury. Early clinical trials are underway with some stem cell treatments, but there are many possible stem cell entities that still need to be evaluated for safety and efficacy.

3. **Health and quality of life for individuals living with SCI**

   SCI is a life-long condition and those with an SCI have a decreased life expectancy compared with uninjured individuals.[4] Besides lack of mobility and sensation, SCI can directly result in bladder and bowel dysfunction, autonomic dysfunction, and neuropathic pain. Other secondary health effects of SCI can include pressure ulcers, depression, and a significant caregiver burden.

   Neuropathic pain remains a very severe consequence of SCI, and available drug treatments are inadequate. How the SCI leads to development of neuropathic pain is not completely understood. Particularly in the context of the national opioid epidemic, finding effective alternatives to pharmacologic interventions for treatment of pain over years of life with SCI is very important.

   Bladder and bowel dysfunction are rated by individuals with SCI as a leading concern.[6] Many interventions targeting restoration of SC function, including electrical stimulation, exercise rehabilitation, and neuroprosthetic devices, are also showing potential for improvements in bladder and bowel function. For example, some evidence suggests that increased movement offered in exoskeleton therapy approaches also improves bladder and bowel function, although more studies are

needed to quantify this effect. In addition, development of neuroprosthetic devices that directly activate nerves controlling urinary function will be ready in the near term for testing in humans.

Biopsychosocial effects of SCI for both the injured individual and their caregivers can be severe. The incidence of depression in individuals with SCI is approximately three times that of the general population and may be even higher in Veterans with SCI.[8] Understanding and addressing this issue is important to improving quality of life for individuals with SCI and their families.

RESEARCH FUNDING LANDSCAPE

Today's medical research environment is dynamic. New research data sets are being created and made available to researchers at an ever-faster rate, and new technologies are emerging that will enable research that is impossible today. Funding for SCI research comes from a variety of sources through a variety of programs. Many are funded by the Federal Government through the NIH, VA, and CDMRP (and other DoD components). In FY17, the SCIRP was the second largest federal funder of SCI research behind the NIH (see Table 1). Although these are the three leading federal funders of SCI research, the National Science Foundation supports important basic and neuroprosthetic/robotics research, and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) funds projects in support of its mission to improve the abilities of individuals with disabilities to fully participate in their communities. An important NIDILRR effort is the National Spinal Cord Injury Statistical Center, which provides key information on SCI epidemiology used by the SCIRP and other programs. Funding for SCI research is also available through state and non-governmental organizations. In the United States, these include the Craig H. Neilsen Foundation (CHNF), the Christopher and Dana Reeve Foundation (CDRF), and the Paralyzed Veterans of America, with an estimated joint FY17 funding for SCI research of $30-50M.

Table 1: Estimated Annual Expenditures for SCI Research in 2017, Based on Information from Program Directors and the NIH Research Portfolio Online Reporting Tool (RePORTER)

Organization	SCIRP	VA	NIH
2017 Investment in SCI Research	$26.6M	$25.1M	$74.3M

The SCIRP must fit within this environment to maximize the value and impact of SCIRP-funded research. To address this challenge, the SCIRP has Programmatic Panel member representation from major U.S. SCI funding entities, including the NIH's National Institute of Neurological Disorders and Stroke, the VA, the Paralyzed Veterans of America, and the CHNF and CDRF (the yearly SCIRP Programmatic Panel member lists are posted online at http://cdmrp.army.mil/scirp/). The SCIRP regularly coordinates with program staff; reviews funding efforts by these and other state, national, and international SCI organizations; and incorporates that information into the annual Vision Setting and other program planning activities. The SCIRP is continually looking to improve on this effort through outreach to funding and advocacy groups. Examples of initiatives being tracked by the SCIRP include the CDRF campaign to move epidural stimulation forward and the VA's Gordon Mansfield Spinal Cord Injury Translation Collaborative Consortium to advance the field of regenerative rehabilitation in SCI. SCIRP program staff also participate in NIH workshops, including the upcoming SCI 2020: Launching a Decade for Disruption in Spinal Cord Injury Research (February 2019).

Through these efforts and program staff attendance and involvement at national meetings, including those of the Society for Neuroscience, the National Neurotrauma Society, and the American Spinal Injury Association, the SCIRP works with the SCI community to maximize the impact of public and private funding in advancing research and clinical care in SCI.

STRATEGIC DIRECTION

The SCIRP evaluates program progress and revisits the strategic direction annually using input from scientific experts, particularly members of the Programmatic Panel, in-progress review of funded research, and coordination across funding agencies. Each year, the SCIRP strives to target research funding to the highest program priority needs and to areas with the most potential for improving the lives of those with SCI.

The SCIRP maintains awareness of the unique needs of military Service members and Veterans with SCI through engagement of military medical officers and Service-injured consumer reviewers at peer and programmatic reviews, as well as the involvement of program staff from the Clinical and Rehabilitative Medicine and Combat Casualty Care Research Programs. Examples of the SCIRP's response to militarily relevant needs include a continued investment in acute SCI management—where SCIRP leads all other U.S. funding entities in support—as well as a focus on the experience of military Service members, Veterans, and their family members and caregivers in quality of life research.

The SCIRP continues to incorporate input from individuals with SCI. In addition to the involvement of SCI consumer reviewers at peer and programmatic review, starting in FY19 SCIRP requires investigators proposing translational and clinical studies to include consumer advocates in the research team throughout the planning and implementation of the research project.

STRATEGIC PRIORITIES

Considering the Congressional intent for the SCIRP, the current research and funding landscape, and military relevance, SCIRP Programmatic Panel members have identified the following five near-term program research priorities (listed below, ***italics***) that are aligned with and address key gaps in the three major areas of traumatic SCI across the continuum of care, as described in the State of the Science section (**underlined**). The SCIRP plans to invest in these five priorities through the solicitation of innovative and impactful research (contingent upon the availability of future appropriations) and has incorporated these priorities into its FY19 funding opportunities.

- ***Preserving and protecting tissue early after injury:*** **Early and acute care**

  Fund research to develop and evaluate early therapeutic approaches (device and pharmacological) that can lead to improved neurological outcomes after SCI. Research should address gaps in optimal acute injury management and effective neuroprotective interventions. Research to stabilize SCI in the prehospital environment and during transport—an area of particular military relevance—is encouraged.

- ***Biomarkers:*** **Early and acute care/Rehabilitation and restoration of function/Health and quality of life**

  Fund studies to identify and validate SCI biomarkers for diagnosis, prognosis, and evaluation of treatment efficacies. A need for better biomarkers, which could include imaging and other modalities, was identified as a gap that spans all three SCI research areas. The biomarkers may be used for diagnosis/prognosis after the original injury; to evaluate the efficacy of interventions; and/or to identify the best single or combination of treatments for individuals (personalized medicine). Research addressing this priority area will have the potential to better direct treatment for improved patient outcomes.

- ***Rehabilitation and regeneration:*** **Rehabilitation and restoration of function**

  Fund research aimed at maximizing the function of the residual spinal neural circuitry, including harnessing neuroplasticity and recovery. The FY19 SCIRP focus area developed to address this priority supports research at any time after injury. Supported studies include neuroprostheses, pharmacologic and exercise interventions, exoskeleton training, and other approaches. There are opportunities for research in this area to improve function in individuals with SCI. Supported research will identify new interventions, and fill gaps in our understanding of mechanisms of action, dosing, and the best combinations of existing therapies.

- ***Bladder dysfunction, bowel dysfunction, and neuropathic pain:*** **Health and quality of life**

  Fund research addressing these three significant problems across the full life span and from acute to chronic injury for the individual with SCI. Research may address gaps in knowledge about the mechanisms of one or more of conditions such as bladder dysfunction, bowel dysfunction, or neuropathic pain in individuals with SCI, or propose the development and testing of interventions, including drugs and devices. Results have the potential to improve patient health and quality of life.

- ***Psychosocial issues relevant to individuals with SCI and their caregivers:*** **Health and quality of life**

  Fund research to identify and develop strategies for managing psychosocial issues that prevent a full return to engagement after SCI. Research supported in the FY19 SCIRP focus area aligned with this priority must show clear relevance to the needs of Service members and Veterans, particularly with regard to depression, resiliency and self-management. Because SCI affects not just the injured individual, but their families as well, supported research includes studies of caregivers.

INVESTMENT STRATEGY

The FY19 SCIRP investment strategy was developed to support progress within these targeted areas by offering four award mechanisms aligned with the SCIRP vision of advancing the treatment and management of SCI. Figure 4 shows the four funding opportunities offered in FY19 as they combine to move research forward toward patient impact.

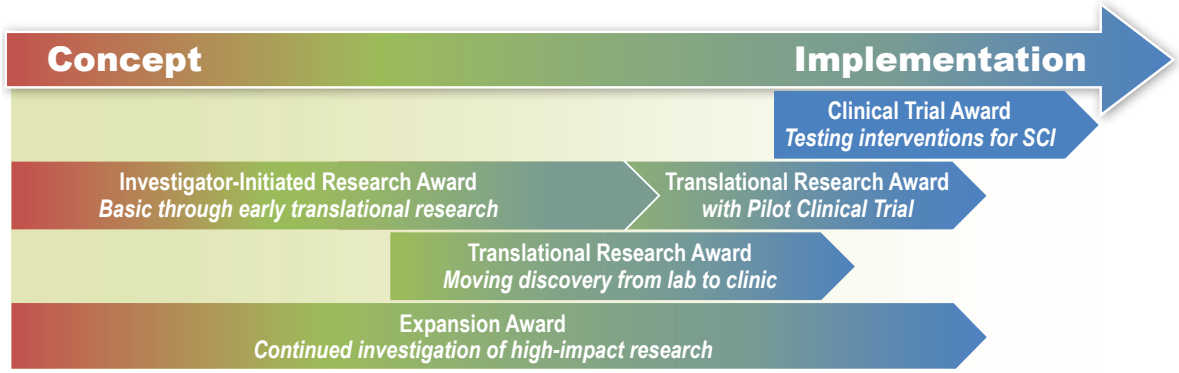
The Clinical Trial Award (CTA) supports rapid implementation of clinical trials with the potential to have a significant impact on the treatment or management of SCI.

The Investigator-Initiated Research Award (IIRA) supports basic through early translational research. Investing through this award mechanism allows innovative hypothesis development and testing by investigators in animal and human subject studies (although not clinical trials). Research outcomes from the IIRA could include novel solutions in key priority areas and lead to research moving into the translational phase. The potential for impact is a significant criterion for evaluation in this funding opportunity.

The Translational Research Award (TRA) is intended to move promising discoveries forward into clinical applications. The TRA allows for inclusion of small pilot clinical trials in the award, with the goal of facilitating this movement. The intention is to support completion of preclinical studies and performance of first-in-human pilot studies to gather the information that will be required to plan and initiate a full clinical trial.

The Expansion Award (EA) supports continued investigation and further development of high-impact research projects that were previously funded by the SCIRP.

Figure 4: FY19 SCIRP Funding Opportunities



MEASURING PROGRESS

Program evaluation will be conducted on an ongoing basis using a number of parameters, including the following:

- Assessing Research Activity
  - o Quantity and quality of grant applications received
  - o Awards funded in each priority area
  - o Investigators and institutions that engage in SCIRP-sponsored research projects
- Assessing Scientific Output
  - o Publications
  - o Patent applications and patents
- Clinical Progress
  - o Therapeutic agents identified and/or tested
  - o Therapeutic devices designed and validated
  - o Diagnostic tools and methods developed
  - o Investigational New Drug/Investigational Device Exemption applications submitted to and approved by the FDA
  - o Clinical practice guidelines
  - o Clinical trials resulting from SCIRP-funded projects

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