The Interdisciplinary SCI Center was funded to strengthen spinal cord injury (SCI) research within the state of South Carolina. The plan was to help develop interdisciplinary research bridging the gap between basic science and applied research, consistent with the NIH initiative. The goals included strengthening interdisciplinary research, positioning investigators to increase overall funding, and initiate novel research with an interdisciplinary focus. Initially, Dr. Krause and Dr. Kindy were the primary investigators on the award. Dr. Banik took over for Dr. Kindy in the role of Associate Scientific Director.

The program of research has been successful over the years, although the original three-year timeline was extended considerably. The initial proposal was built around motion analysis which is a key feature to rehabilitation research, with the explicit goal of developing animal motion research. This goal was accomplished with a key faculty member, Dr. Tasos Karakostas, who was the sole engineer of the laboratory and ultimately published the results and credited to the SCI research fund (Karakostas, Hsiang, Boger, Middaugh, & Granholm, 2013). Although Dr. Karakostas left the state before the work was completed, human motion analysis continues to be a key component of the work at the Medical University of South Carolina. Facilities were upgraded by the University at no additional cost to the SCIRF, and these facilities were instrumental in subsequent recruitment. The investments in motion analysis technology ultimately contributed to the development of the Center for Rehabilitation Research in Neurological Conditions and helped facilitate the recruitment of Dr. Bowden and Dr. Gregory, both of whom work with more advanced zero gravity technology.

The work of the Interdisciplinary Center continued to evolve over the years with an emphasis placed on bridging the gap between animal and human research, with critical input and effort from Dr. Banik. The initiatives included the investigation of novel concepts of stress based measures of function, including the first pilot data collection using the allostatic load framework (a physiologic based theory of stress) that measures five types of biomarkers: (1) anthropometric measures and (2) cardiovascular and respiratory, (3) metabolic, (4) neuroendocrine, and (5) immune system biomarkers (Juster, McEwen, & Lupien, 2010). This pilot study was published (Krause et al., 2014). A review article was also published on oxidative stress and DNA damage (Smith, Park, Krause, & Banik, 2013).

We also conducted pilot investigations of both human and animal telomeres. This included collecting pilot data on 30 individuals with SCI, many of whom lived a significant distance from MUSC where the data were collected. Comprehensive data was collected on 11 different biomarkers, as well as DEXA scans of bone density. Stored blood was used for the telomere analysis, which, at the time, had not been done with SCI.

Work in Dr. Banik’s laboratory is summarized below the remainder of this report and has led to successful extramural funding from both NIH and VA Research Programs and helped develop strategies for the treatment of SCI. To this end, the progress made in the past years has been highly significant. For example, low dose estrogen (Premarin) has been taken into the clinic for a safety trial at MUSC in collaboration with Dr. Abhay Varma, MD, a neurosurgeon and SCI researcher. This will be further tested with estrogen delivered in a nanoparticle gel; this delivery system has been used in experimental rat SCI. Calpain inhibitor SNJ1945 has been developed and tested in animals with SCI. Combination therapy, which was previously investigated, has been discontinued for the time due to lack of funding. Another new project developed a couple of years ago generated interesting data and continues. These projects have many publications, reviews, and book chapters over this period (2009 to present), and results were
presented at invited seminars and at national and international meetings. Research also generated extramural funding.

1. **Effect of Estrogen in SCI**: We recently demonstrated beneficial effects of estrogen, a multi-active agent, as a neuroprotectant. Estrogen blocks the degenerative process in rats with acute and chronic SCI. This work was continued utilizing very low dose estrogen (Premarin, 1-10µg/kg body weight) to minimize the side effects of high dose estrogen administration, including feminizing effects, in animals with SCI. The low dose estrogen reduced inflammation, protected cells, preserved axons and myelin, and improved locomotor function. These very encouraging data led us to examine the effects of low dose estrogen delivered by nanoparticles in both acute and chronic SCI. Data generated are encouraging, and this work continues in the laboratory. The efficacy of this nanoparticle estrogen delivery for the treatment of SCI has only been demonstrated in our laboratory.

2. **Safety Trial with Nanoparticle Delivery of Estrogen in Clinic**: All five individuals with SCI participating in the safety trial for estrogen treatment survived. However, since severe SCI individuals are prone to develop deep vein thrombosis (DVT), whether estrogen caused DVT was not clear. To continue this study, we have examined the efficacy of very low dose estrogen delivery via nanoparticle for ameliorating damage to cells in vitro and in rat SCI in vivo. The nanoparticle development, in collaboration with Clemson University Bioengineering Department, is very promising and seems to demonstrate the feasibility of this new delivery system. We are excited about the prospect of estrogen therapy and believe that, in the very near future, delivery of estrogen via nanoparticle will be taken to the clinic for trial. To do such a clinical trial, we will apply to NIH for funding resources. Since the goal of the SCIRF is to take basic research into the clinic, we sincerely hope the SCIRF will support a pilot clinical trial study with estrogen.

3. **Combination Therapy for SCI**: Our long-standing NIH funded grant has generated the data on the feasibility of using melatonin, methylprednisolone (MP), and calpain inhibitor for pharmacological intervention. A combination of triple treatment using melatonin, MP, and calpain inhibitor in rat SCI has demonstrated much better improvement in locomotor function. These preliminary data are very promising for SCI therapy. Because both melatonin and MP are FDA approved, with future approval of calpain inhibitor this therapeutic approach has great potential for use to treat individuals with SCI. We want to test this novel therapeutic strategy thoroughly to fulfill the goal of finding a cure and/or ameliorating dysfunction in SCI. This project is currently halted due to lack of funding; therefore, resources have to be generated to achieve this goal.

4. **Receptor Agonist-Mediated Protective mechanisms of estrogen and melatonin**: Estrogen and melatonin receptor agonists-mediated pathways will be studied both in vitro and in SCI in vivo. These agonists could be potential alternative therapeutic agents for treatment of SCI. Since agonists are three times more sensitive than the parent agent, the use of receptor agonists will reduce the potential for side effects of treatment with estrogen and melatonin, as such.

5. **Telomere and Telomerase**: We have started to investigate whether any changes in telomere length and telomerase activity are found in human SCI blood samples as well as in blood from rats following SCI. To maintain telomere length is very important for cell survival. The goal of this project is to establish if any relationship exists between telomere length and severity of injury and extent of dysfunction/disability. For human studies, we are trying to obtain blood from individuals with SCI so that the enzyme activity can be determined. As we wait, studies on telomere and telomerase in SCI rats have generated very encouraging preliminary data. Telomere length may be correlated with extent of severity and time following injury as well as cell death and other detrimental parameters. This work is continuing. We are looking into whether treatment with nanoparticle estrogen can reverse this relationship and maintain the telomere length. Since telomere shortening leads to cell death, maintaining telomerase activation, which extends the life span of a cell, is important. Activation of telomerase can improve the longevity of cells as well as the quality of life not only in individuals with SCI, but also in the general population.
The above studies are in progress and will be continued. Studies listed and described received partial support from the SCIRF for Drs. Nozaki, Ray, and Varma and contributed significantly to the advancement of our understanding of the mechanisms involved in degeneration and protection of the spinal cord following injury.

In summary, the work of the Interdisciplinary SCI Center has continued since the original funding. The funding has been essential to the development of research that is interdisciplinary, including human and animal studies of innovative constructs including telomeres and telomerase.

References


