

# **TR2-01785: Repair of Conus Medullaris/Cauda Equina Injury using Human ES Cell-Derived Motor Neurons**

**Recommendation:** Not recommended for funding

**First Year Funds Requested:** \$606,929

**Total Funds Requested** \$1,614,441

## **Public Abstract (provided by applicant)**

Injuries to the spinal cord commonly result from motor vehicle accidents, traumatic falls, diving, surfing, skiing, and snowboarding accidents, other forms of sports injuries, as well as from gunshot injuries in victims of violent crimes. Injuries to the anatomically lowest part of the spinal cord, the lumbosacral portion and its associated nerve roots commonly cause paralysis, loss of sensation, severe pain, as well as loss of bladder, bowel, and sexual function. Lumbosacral injuries represent approximately one-fifth of all traumatic lesions to the human spinal cord. As a result of the direct injury to the lumbosacral portion of the spinal cord, there is degeneration and death of spinal cord nerve cells, which control muscles in the legs as well as bladder, bowel, and sexual function. No treatments are presently available in clinical practice to reverse the effects of these devastating injuries. In order to reverse the loss of function after lumbosacral spinal cord injury, replacement of the lost nerve cells is required. Recent research studies have identified some properties that are shared by spinal cord neurons responsible for muscle and bladder control. Human embryonic stem cells can now be prepared in research laboratories to develop properties that are shared between nerve cells controlling muscle and bladder function. Such nerve cells are particularly at risk of degeneration and death as a result of injuries to the lumbosacral spinal cord. Human embryonic stem cells, which have undergone treatment to obtain properties of muscle and bladder controlling nerve cells, are now very attractive development candidates for new cell replacement therapies after lumbosacral spinal cord injuries. The proposed feasibility studies will study the properties of such cells in a clinically relevant rat model for lumbosacral spinal cord injuries. In Specific Aim 1, we will determine whether ACUTE transplantation of human embryonic stem cells, which have been treated to develop properties of specific lumbosacral spinal cord neurons, may replace lost nerve cells and result in a return of bladder function in a rat model of lumbosacral spinal cord injury and repair. In Specific Aim 2, we will determine whether DELAYED transplantation of human embryonic stem cells, which have been treated to develop properties of specific lumbosacral spinal cord neurons, may replace lost nerve cells and result in a return of bladder function in a rat model of lumbosacral spinal cord injury and repair. A variety of functional studies will determine the effect of the cell transplantation on bladder function, walking, and pain. We will also use detailed anatomical studies to determine in microscopes whether the transplanted cells have grown processes to connect with pelvic target tissues, including the lower urinary tract. If successful, the proposed experiments may lead to a new treatment strategy for patients with lumbosacral spinal cord injuries.

## **Statement of Benefit to California (provided by applicant)**

There are presently about 250,000 patients living with neurological impairments from spinal cord injuries (SCIs) in the United States, and approximately 11,000 new cases present every year. SCIs typically result in paralysis, loss of sensation, pain as well as bladder, bowel, and sexual dysfunction. No successful treatments are available to reverse the neurological deficits that result from SCI. Common causes for SCIs include car and motorcycle accidents, skiing, diving, surfing, and snow boarding injuries, traumatic falls, sports injuries, and acts of violence. California medical centers encounter a large proportion of the overall cases in the U.S. because of our large population, extensive network of freeways, and an active life style with recreational activities taking place both along the Californian coastline and in the mountains. The proposed development candidate feasibility project will capitalize on recent progress in human stem cell science and surgical repair of conus medullaris/cauda equina (CM/CE) forms of SCI. Human embryonic stem cell-derived neurons and neuronal progenitors, which express the transcription factor Hb9, will be transplanted into the conus medullaris in attempts to replace lost motor and autonomic neurons after a

lumbosacral ventral root avulsion injury in rats. Surgical replantation of avulsed lumbosacral ventral roots into the spinal cord will also be performed in this clinically relevant model for CM/CE injury and repair. If successful, our development candidate may reinnervate muscles and pelvic organs, including the lower urinary tract after CM/CE forms of SCI. Return of functional bladder control represents one of the absolute top priorities among the spinal cord injured population (Anderson, J Neurotrauma, 2004; 21, 1371-83). Successful recovery of bladder function after SCI is expected to have very significant impact on the quality of life of spinal cord injured subjects and markedly reduce health care costs. Recovery of bladder function in spinal cord injured subjects would markedly reduce or eliminate the need for intermittent bladder catheterizations and indwelling bladder catheters. The number of visits in physicians' offices and already over-crowded California emergency rooms for bladder infections and other complications would be markedly reduced, thereby significantly reducing health care costs for both patients and our state. Improved neurological function among the SCI population is also expected to reduce care giver needs, thereby further reducing health care costs. The increased independence that will result from improved bladder control and concomitant possible recovery of other neurological functions, for instance in transfers and locomotion, will promote return to and participation in the work force for many individuals with SCI. These effects are also expected to bring a very positive effect to the California economy and increased quality of life for those living with an SCI.

## Review

This is an application for a development candidate feasibility (DCF) award that focuses on developing a human embryonic stem cell (hESC)-derived cell therapy for conus medullaris/cauda equina (CM/CE) injury, a type of injury to the lumbosacral (lower) spinal cord and its associated nerve roots. CM/CE injuries result in paralysis, sensory deficits, neuropathic pain, and bladder, bowel, and sexual dysfunction due to the degeneration and death of motor and autonomic neurons. The applicant proposes that hESC-derived motor and autonomic neurons can be used to replace lost neurons and augment functional reinnervation of the lower urinary tract. In order to test this, the applicant plans to transplant hESC-derived motor and autonomic neuron precursors into the lumbosacral spinal cord of rats following a lumbosacral ventral root avulsion (VRA) injury and subsequent root replantation surgery. Following transplantation, the rats will be monitored for behavioral, anatomic, and functional improvements with the expected outcome to be reinnervation of the lower urinary tract and improvement of bladder function. The applicant proposes to perform the cell transplant and root replantation surgery treatment both soon after injury (Aim 1) and after a period of delay following injury (Aim 2).

Reviewers agreed that this proposal addresses an important unmet medical need and could have significant impact on the patient population if successful. Further, the rationale for this approach was viewed as sound, since traumatic CM/CE injuries result in degeneration and death of both motor and autonomic neurons, making this condition a suitable target for stem cell replacement therapy. One reviewer noted that the rationale would have been strengthened by the inclusion of data demonstrating regenerative benefit is possible with the proposed therapeutic cell population. Reviewers considered the focus on a relatively nearer and simpler target in spinal cord injury (SCI), reinnervation of the bladder, an advantage of the proposal.

Reviewers found the experimental plan to be generally well designed, and they appreciated the solid electrophysiological outcome measurements for bladder function. However, reviewers did not think the proposed experimental goals were achievable. In particular, reviewers were not convinced by the preliminary data that effective, anatomically accurate and topographically precise reinnervation could be achieved with the transplanted cells; the preliminary data suggested that the transplanted cells exerted a trophic effect rather than participating in direct reinnervation. Additionally, the data supporting survival and migration of neural precursor cells were not compelling, and reviewers felt that both activities would be necessary for reinnervation to be possible. Furthermore, the applicant did not address potential inhibitory effects of myelin on reinnervation, and alternate plans were not discussed in the event that the proposed immunosuppression regimen proved ineffective.

In addition to these critical concerns regarding the ability of the team to achieve the stated goals, reviewers expressed strong reservations about other aspects of the project's feasibility. Limited preliminary data demonstrating the ability of the research team to produce the therapeutic cell populations were included in the proposal. This deficiency raised serious doubts about production and purity of motor neurons. Additionally, data demonstrating the production of autonomic neurons were completely lacking.

Agenda Item # 4  
11/11/10 ICOC Meeting

The reviewers praised the principal investigator (PI) and research team, calling them well suited to carry out the proposed research. The PI has extensive experience in SCI and is an expert in the motor and autonomic pathways associated with the CM/CE. The collaborators provided first-rate expertise in motor neuron and stem cell biology. There was some concern as to whether the team possessed adequate expertise in the field of cell therapy for the damaged spinal cord.

Overall, reviewers recognized the potential impact of this project for developing a treatment for CM/CE injury. The proposal was based on sound rationale and featured a well-designed experimental plan and qualified research team. However, reviewers did not think the proposed research goals were achievable due to a lack of preliminary data supporting the feasibility and achievability of the objectives and, consequently, did not recommend this DCF award application for funding.

**PROGRAMMATIC REVIEW**

A GWG member proposed a motion to assess the level of enthusiasm among the panel for considering this application from a programmatic perspective. The GWG did not support a motion to consider the application further.

**The following Working Group members had a conflict of interest with this application:**

- none