Spinal ischemic paraplegia: modulation by human embryonic stem cell implant.

Reporting Period: Year 2

Transient spinal cord ischemia is a serious complication associated with aortic cross clamping (a surgical procedure required for the repair of aortic aneurysm). Neurological dysfunction resulting from transient spinal cord ischemia may be clinically expressed as paraparesis, fully-developed spastic paraplegia, or flaccid paraplegia. In spastic paraplegia, the underlying spinal pathology is characterized by a selective loss of inhibitory cells (neurons) in the ischemia-injured spinal cord. That loss of inhibition produces increased muscle tone (i.e. spasticity). While there are some current pharmacological treatments for spasticity that provide a certain degree of functional improvement, there are no effective therapies that lead to clinically-relevant, long-lasting recovery. One of the therapeutic approaches pursued by our group is the characterization of functional changes after spinal cord transplantation of neuronal cells previously generated in culture with the goal of replacing missing inhibitory neurons in the spinal cord. In our recent experiments, we characterized the survival and differentiation of human embryonic stem cell-derived neural precursors that were grafted into the spinal cord of rats with a previous spinal ischemic injury. Our initial data demonstrate that spinal grafting of neural precursors generated from 3 independent human embryonic stem cell lines is associated with long-term cell engraftment of grafted cells. A significant population of the grafted cells displayed neuronal differentiation, progressive maturation, and expression of markers which are typical for mature, functional human neurons. Initial analysis of grafted cells also indicated the development of functional connectivity between transplanted neurons and surviving neurons of the recipient. A significant advancement in our effort to characterize the effect of such a treatment was the use of a sorting technique which permits the generation of large quantities of highly-purified neural precursors. The capacity to generate such large quantities of pure cell populations is particularly important in our large preclinical animal model (minipig), which is essential to move this therapeutic approach to clinic. In addition, we characterized an efficient cell freezing protocol. The sorting and freezing techniques together allow large quantities of identical cell populations to be frozen for future transplantation, ensuring a group of animals receives an identical cell population. Our plan for the next year is to perform long-term functional recovery studies in our minipig model of spinal ischemia.

Reporting Period: Year 3

Transient spinal cord ischemia is a serious complication associated with aortic cross clamping, i.e., the procedure required to replace aortic aneurysm. The major neurological deficit resulting from spinal ischemic injury is the loss of motor function in lower extremities, also called paraplegia. The pathological mechanism leading to the loss of function is the result of progressive death of spinal cells (i.e., neurons) in the affected region of the spinal cord. At present there is no effective therapy for spinal ischemia-induced paraplegia. In our previous completed studies, we have characterized the survival and neuronal maturation of human embryonic stem cell derived neural precursors analyzed at 2 weeks to 2 months after spinal transplantation in spinal ischemia-injured rats. A comparable survival and maturation was seen compared to fetal human spinal cord-derived cells. In our next studies, we will define the therapeutic potency of spinally grafted ES-NPCs once cells are grafted into the spinal cord of immunodeficient rats (i.e., animals which do not require immunosuppression) and the effect of cell grafting assessed for up to 4 months after cell transplantation. In subsequent studies, the degree of treatment effect will be studied in continuously immunosuppressed minipigs with previous spinal ischemic injury.

Reporting Period: Year 4

Transient spinal cord ischemia is a serious complication associated with aortic cross clamping, i.e., the procedure required to replace aortic aneurysm. The major neurological deficit resulting from spinal ischemic injury is the loss of motor function in the lower extremities, also called paraplegia. The pathological mechanism leading to the loss of function is the result of progressive death of spinal cells (i.e., neurons) in the affected region of the spinal cord. At present there is no effective therapy for spinal ischemia-induced paraplegia. In our previous completed studies, we have characterized the survival and neuronal maturation of
human embryonic stem cell-derived neural precursors grafted into the lumbar spinal cord in immunodeficient rats and have demonstrated good tolerability of long-term immunosuppression in rodents and minipigs after using subcutaneously implanted tacrolimus pellets. In our ongoing studies, our goal is to characterize the effect of clonally expanded embryonic stem cell-derived neural precursors after spinal grafting in long-term immunosuppressed rats and minipigs and immunodeficient rats with previous spinal ischemic injury.

Spinal ischemic paraplegia: modulation by human embryonic stem cell implant.

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Public Abstract: Ischemia-induced paraplegia often combined with a qualitatively defined increase in muscle tone (i.e. spasticity and rigidity) is a serious complication associated with a temporary aortic cross-clamping (a surgical procedure to repair an aortic aneurysm). In addition to spinal ischemic injury-induced spasticity and rigidity a significant population of patients with traumatic spinal injury develop a comparable qualitative deficit i.e. debilitating muscle spasticity. At present there are no effective treatment which would lead to a permanent amelioration of spasticity and rigidity and corresponding improvement in ambulatory function. In recent studies, by using rat model of spinal ischemic injury we have demonstrated that spinal transplantation of rat or human neurons leads to a clinically relevant improvement in motor function and correlates with a long term survival and maturation of grafted cells. More recently we have demonstrated a comparable maturation of human spinal precursors grafted spinally in immunosuppressed minipig. In the proposed set of experiments we wish to characterize a therapeutical potential of human blastocyst-derived neuronal precursors when grafted into previously ischemia- injured rat or minipig spinal cord. Defining the potency of spinally grafted hESC-derived neuronal precursors in two in vivo models of spinal ischemic injury serves to delineate the differences and/or uniformity in the cell maturation when cells are transplanted in two different animals species and can provide an important data set for future implications of such a therapies in human patients.
Traumatic or ischemic spinal cord injury affect a significant number of people and in majority of cases can lead to a variable degree of motor dysfunction (such as paraparesis or paraplegia) and often combined with increased muscle tone (i.e. spasticity and rigidity). In contrast to other organ systems the central nervous system and spinal cord in particular has minimal or no neuron-regenerative capacity and therefore if a significant population of spinal cord neurons or fibers is lost the resulting deficit is permanent and irreversible. At present there is no effective therapy which would lead to a clinically relevant neurological improvement in patients with ischemia or trauma-induced paraplegia. Initial experimental data using paraplegic rats show that spinal grafting of rat or human neuronal precursors can provide a significant amelioration of spasticity and lead to improved ambulatory function. In the proposed set of experiments we wish to characterize a therapeutical potential of human blastocyst-derived neuronal precursors when grafted into previously ischemia- injured rat or minipig spinal cord. If proven effective such a treatment can potentially be used in patients with spinal ischemic paraplegia or in patients with other spinal injury-related dysfunction associated with a region-specific neuronal loss.