Spinal cord injury (SCI) is a devastating disease that often results in permanent paralysis below the level of injury. There are approximately 250,000–400,000 people living with SCI in the United States alone and about 7,800 new cases per year with no real cure. SCI is not a fatal injury; life expectancies are average. However, these individuals’ cost of living is greatly increased as a result of frequent doctor visits, wheelchair costs, and the necessity of adapted cars or homes. In addition to these increased costs, some also need in-house nurses or live-in family members who help them with daily activities such as eating, bladder control, and bowel movements, which also greatly increase their cost of living as well as dampen their independence and psychological state. In 2004, Kim Anderson published a paper showing that improving quality of life such as regaining partial limb function or bladder control is the top priority for persons with SCI, rather than actually walking again. Therefore, stem cell based therapies have become increasingly popular due to their ability to not only replace lost cell types but also aid in regeneration and recovery of function in hopes of improving one or more of these issues.

In 2005 our lab was the first to derive high purity oligodendrocyte progenitors (OPCs) from human embryonic stem cells (hESCs) and also transplant them into SCI rats (Keirstead et al, 2005). During the initial stages of SCI, large amounts of oligodendrocytes die and the myelin that they provide to axons is lost. This demyelination leads to impaired conductances and attenuated action potentials of axons, which results in paralysis (Nashmi et al, 2000). Our OPC-derived hESCs were able to integrate into the injured spinal cord, differentiate into mature oligodendrocytes, and reinvest lost myelin (or remyelinate). This was also accompanied by a significant increase in locomotor recovery in transplanted animals and helped show the benefit of cellular transplant therapies for SCI. Due to this work, this year Geron Corporation was approved for the first clinical trial in humans using stem cell based cells for SCI, helping pave the way for other similar stem cell based transplant therapies.

Although clinical trials are underway for hESC-derived OPCs for SCI patients, we still do not know the exact mechanism of how these cells are able to increase the locomotor recovery that we see. In our previous studies we saw a significant increase in remyelination in transplanted animals, but we could not prove that this alone was responsible for the increases in locomotion. In fact, since then Geron has found that these hESC-derived OPCs secrete a number of growth factors that play a role in sparring (Zhang et al, 2006), concurrent with our recent findings of increases in neuronal sparring and sprouting of axons both in vitro and in SCI rats (data not published yet). This leads to the question of whether the locomotor recovery seen in these rats was due to the increases in remyelination or the growth factor related sparring effects.
To answer this we have obtained ESCs from shiverer and wild-type (WT) matched mice, and we will be differentiating them into OPCs and transplanting them into SCI rats. Mutant shiverer mice have an autosomal recessive mutation on chromosome 18 that deletes a large portion in the myelin basic protein gene (MBP) (Roach et al, 1983; Molineaux et al, 1986). This inability to synthesize MBP means that the cells from shiverer mice are not able to myelinate axons properly, yet they are similar in every other way to WT cells. We have recently obtained the first stem cells derived from these mutant mice and are planning on differentiating them into OPCs for transplantation studies. By comparing them to their WT counterparts, we will be able to deduce whether the remyelination from these cells or their growth factor related effects are responsible for the locomotor recovery seen in SCI rats.

To carry out this experiment, we will be using our developed protocol for differentiating OPCs from mouse ESCs (data unpublished) and applying this protocol to both the shiverer and WT cells. The differentiation procedure will require large scale differentiation of OPCs from both cell types and supplies from BD Biosciences and will include T75 tissue treated flasks, 15-mL and 50-mL conical tubes, pipettes, and 50-µm cell strainers. Our protocol utilizes different extracellular matrices at different stages that include the use of BD Matrigel™ and poly-D-lysine with laminin. Along the way we will be making sure the shiverer and WT cells perform similarly in differentiation potential, growth factor expression, and maturation (except for MBP expression).

By the end of the in vitro component of this experiment, we will produce an effective tool for further studies pertaining to OPC development and remyelination. This will be the first line of OPCs from shiverer mice providing a useful tool for MBP and remyelination studies. For our purposes, this experiment will answer how our transplanted OPCs increased locomotor recovery. Hopefully these studies will help the current trial underway with Geron and inspire other combinatorial strategies for future SCI therapies that can improve the quality of life of SCI patients.

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