Vanessa Libera
Methods in Neurobiology – Module 11 Case Study

Background:
Sciatic nerve injuries can occur for many reasons, such as a herniated disk in the spine, or a bone spur on the vertebrae, which causes pain from the lower back through the hips and down each leg. Individuals that are at greater risk of sciatica are typically those who are older, obese, occupations with lots of physical labor, those who sit for prolonged periods of time, and diabetics. This nerve over time has the ability to regenerate, however with recurring sciatica, people may eventually experience permanent nerve damage. [1] Often times, regeneration is suboptimal because of the lack of sufficient mature axons reaching their targets. Transforming growth factor beta 1 (TGF-β1) treatment could potentially aid in Schwann cell capacity in order to promote axonal regeneration. [2]

Aim:
To use mouse models infected with *Mycobacterium leprae* to determine if treatment with TGF-β1 will aid the denervated Schwann cells to proliferate and upregulate the expression of regeneration-associated proteins, in turn allowing the nerve to regenerate. [2] Infection with *Mycobacterium leprae* has been shown that the bacterium seeks out nerve cells and has the ability to attack Schwann cells of the PNS. [3]

Plan:
The plan here is to have two sets of mice, where one set is the control and the other will be infected with *Mycobacterium leprae* with sciatic nerve damage and treated with TGF-β1 for six months. To create sciatic nerve damage in our mice, we will use hemostatic forceps, pinching the nerve, and marking the area with charcoal. During this process or crushing the nerve, the mice will be anesthetized, given some pain medication, and allowed some time to recover after the procedure. [4]
Observations will be made over six months between the two sets of mice, particularly paying attention to our set of mice infected with *Mycobacterium leprae* with the crushed sciatic nerve. Both Schwann cells and axonal regeneration will be monitored via in vivo confocal imaging, where the Schwann cells will have GFP and fluoresce green, and the axons pseudo-colored blue. [5] Live images will be taken once every two weeks over the course of 6 months in order to monitor changes during this time.

Applications:
Future applications of this treatment may help thousands of individuals who suffer from sciatica, especially those who suffer from the side effects for much longer than anticipated. However, it must be noted that TGF-β1 can potentially be toxic in the fact that TGF-β1 is overproduced in many pathological conditions such as pulmonary fibrosis, glomerulosclerosis, renal interstitial fibrosis, cirrhosis, Crohn's disease, cardiomyopathy, scleroderma and chronic graft-vs-host disease. It has also been noted that this cytokine also adds to the development of the tumor stroma, angiogenesis and immunosuppression. [6] Therefore, clinical trials may be

risky and will certainly involve lots of caution and a deep understanding of safe levels of TGF-β1 in the body.

Sources:

1. Mayo Foundation for Medical Education and Research. (2020, August 1). *Sciatica*. Mayo Clinic. Retrieved November 16, 2021, from https://www.mayoclinic.org/diseasesconditions/sciatica/symptoms-causes/syc-20377435.

2. Sulaiman, W., & Nguyen, D. H. (2016, October). *Transforming growth factor beta 1, a cytokine with regenerative functions*. Neural regeneration research. Retrieved November 16, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5116823/.

3. Rambukkana, A. (2000, November 13). *Researchers find how leprosy bacterium selects and attacks nerves*. The Rockefeller University. Retrieved November 16, 2021, from https://www.rockefeller.edu/news/4215-researchers-find-how-leprosy-bacterium-selectsand-attacks-nerves/.

4. Bauder, A., & Ferguson, T. (2012, February 22). *Reproducible Mouse Sciatic Nerve Crush and Subsequent Assessment of Regeneration by Whole Mount Muscle Analysis*. Jove. Retrieved November 16, 2021, from https://www-jove-com.proxy1.library.jhu.edu/t/3606/reproducible-mouse-sciatic-nerve-crush-subsequent assessment.

5. Hayashi, A., Koob, J. W., Liu, D. Z., Tong, A. Y., Hunter, D. A., Parsadanian, A., Mackinnon, S. E., & Myckatyn, T. M. (2007, June 19). *A double-transgenic mouse used to track migrating Schwann cells and regenerating axons following engraftment of injured nerves*. Experimental neurology. Retrieved November 16, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2000857/.

6. Prud'homme, G. J. (2007, August 27). *Pathobiology of Transforming Growth Factor β in cancer, fibrosis and immunologic disease, and therapeutic considerations*. Nature News. Retrieved November 16, 2021, from https://www.nature.com/articles/3700669#:~:text=Transforming%20growth%20factor%20β%20(TGF,regulator%20of%20the%20immune%20response.