SAB reviewer exchange with Mark Anderson for his endParalysis proposal

Reviewer 1: It is not clear that the more severe crush to 0.5 mm gap has been performed by this group on NHP, but examining animals weekly for runway and ladder walking will inform them about the course of long-term severity of functional loss and potential for spontaneous recovery.

Anderson: The reviewer is correct that the 0.5mm crush has not yet been performed by us. We choose this severity because we feel that the 1mm crush does not produce a severe enough deficit in hindlimb stepping. As noted by the reviewer, this will be kinematically recorded weekly to track the degree of recovery.

Reviewer 1: Based upon that information it may be that starting an intervention in Aim 2 with a post-injury period shorter than 4 months but with a longer post-treatment period may be important to consider.

Anderson: We respectfully disagree. From our experience it takes around 3 months for the NHPs to behaviorally plateau. Performing our regenerative intervention past this plateau is critical, as we want to ensure that the effects of our regenerative intervention are responsible for any change in hindlimb function, rather than being attributed to spontaneous recovery.

Reviewer 1: While the proposal focuses on recovery of locomotor function, it would be beneficial for the group to make note of possible autonomic activities being affected, such as bladder and bowel function or the ability to respond to temperature changes.

Anderson: We agree with the reviewer and monitor all NHPs for bladder and bowel function.

Reviewer 1: Some mention of possible application to treatment of cervical level injuries also would be appreciated since these represent the greater number of human acute injuries that result in severe impact on arm and hand use and respiration. It is a lot to ask from a short proposal, but these are things to keep in mind as progress is being made with the initial studies.

Anderson: We agree with the reviewer that the application of regenerative interventions to cervical injuries is among the most important aspects of SCI research and is something that our lab is currently working on in rodent models. Our plan is to proceed to NHP models once this is ready. However, at the moment, it is beyond the scope of this proposal.

Reviewer 2: First, monkeys may lose bladder and bowel movement control after a severe bilateral incomplete crush SCI in primates, which may be inhumane.

Anderson: Respectfully, this comment is incorrect. First, our experience shows there is no loss of bowel function in this model of SCI. Second, NHPs do temporarily lose bladder control, but this recovers within the first week. Our NHP facility is able to manually massage the bladders to empty during this time and the NHPs are not inhumanely treated.

Reviewer 2: Continuous over-expression of three genes, IGF-1, CNTF, and Spp1 above SCI site may have serious side effects.

Anderson: The reviewer is correct that continuous overexpression of Igf1, Cntf, and Spp1 may have long term side effects. However, delivery of these growth factors in mice and rats showed no deleterious effects over several months (Anderson et al, Nature 2018, Squair et al, Science 2023, Bei et al, Cell, 2016). The proposed experiments are conducted over a similar several month time frame to demonstrate a proof-of-concept that stimulation of these specific neurons can promote their regeneration and facilitate improvements in hindlimb function. This tool may indeed not be what eventually goes into a person, and there will likely be required modifications to the vector to enable the growth factors to be expressed for a limited period of time. Nevertheless, without these initial experiments being performed successfully, progress for chronic SCI will not advance.