We express our gratitude to Seth Holland for choosing our paper recently published in the Journal of Neuroscience for a journal club article and compiling an elegant mini-review about cAMP signalling. Both from our paper and the journal club article, it becomes clear that cAMP has a significant and beneficial effect on spinal cord repair, although the exact downstream signalling mechanisms are still debatable. The cAMP is a key second messenger for many signalling pathways in all types of cells. Therefore, targeting cAMP specifically can introduce unwanted side effects. Our focus on Epac2 protein as a downstream cAMP target explored a possibility to avoid such unwanted side effects but sustaining all positive effects previously observed in cAMP elevation studies. Within this response letter, we would like to focus on some key findings in our paper that were not highlighted by the journal club article. We would also want to clarify a couple of questions/comments raised by Seth regarding our *in vivo* group selection and absence of histological data.

One of the key findings in our paper was that the specific Epac2 agonist (S-220) had a profound effect in modulating the post-injury environment demonstrated in our *ex vivo* model of spinal cord injury, making it more amenable to axonal regrowth. Seth did comment on the evidence of S-220 modulating characteristics of astrocytes and microglia in our paper. However, such vital evidence merits more consideration as a whole in the context of post-spinal cord injury environment. We demonstrated that the S-220 'turbo-charged' injured axons, helping them to regrow, profoundly reduce the inhibitory nature of the environment around the injury site, thus influenced the recovery in that way. Our *ex vivo* evidence showed that S-220 treatment significantly reduced astrocyte and microglial activation at the lesion site, and most strikingly the treatment modulated the morphology and behaviour of astrocytes which seemed to form a one-on-one relationship with regrowing axons. It is plausible that S-220 desensitised regrowing axons to the inhibitory extracellular molecules, as have been shown by cAMP elevation studies. In summary, our paper demonstrates a novel "one-stone-kills-three-birds" strategy for spinal cord repair by S-220.

Regarding the *in vivo* groups and histological data, first we used S-220, which has a very high specificity for Epac2 activation, in our *in vitro* and *ex vivo* studies, to support the above-mentioned evidence. The *ex vivo* model mimics the post-injury environment *in vivo* and allows the screening of neuro-regenerative strategies before moving into *in vivo* testing. We are strong advocates of the 3R's principle (Replacement, Reduction, Refinement) and adopt this principle in our preclinical research. Therefore, as we had already shown in the *ex vivo* model that the effects of the combinatorial Fmoc-based hydrogel and S-220 treatment was significantly better than the gel or S-220 alone, we only selected the combinatorial treatment for the preliminary pilot *in vivo* study, which was conducted upon the request of peer-review referees within a 3-month period.

Spinal cord injury has a complex nature with multiple cell types affecting the severity. Our next main goal is to identify precise intracellular mechanisms both in glial and neuronal cells that underlie their responses to the treatments we describe.

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