Final Report

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Title of Project: *Target therapies for the treatment of acoustic neuroma*

Summary:
Acoustic neuroma, also known as vestibular schwannoma is a space-occupying tumour on the nerve that carries balance information from the inner ear to the brain. As the tumour grows it can cause not only imbalance and dizziness but also loss of hearing, ringing in the ear, and sometimes numbness in the face. Ultimately, if the tumour grows large enough, it can become life threatening by compressing critical parts of the brain. There are only three approaches for vestibular schwannoma, 1) watch and wait, 2) tumour removal, and 3) radiotherapy. At present there are no drug therapies to slow tumour growth or prevent tumour regrowth after surgical removal. This project aimed to use newly developed blocking antibodies against nerve growth factors to slow or even reduce the size of vestibular schwannomas.

Hypothesis vs Findings

***HYPOTHESIS*:**
Inhibition of proNGF, p75NTR, and sortilin using blocking antibodies will **decrease** cell proliferation and **increase** apoptosis (programmed cell death) in cultured vestibular schwannoma cells.

***FINDINGS**:*
Our aim was to examine if newly developed antibodies targeting neurotrophic growth factors could slow or even stop cultured schwannoma cell growth. These antibodies/inhibitors target proNGF, p75NTR, and sortilin. We cultured three different types of cells, a schwann cell line, schwannoma cell line, and dissociated patient-derived primary vestibular schwannoma cells. Figure 1 shows cells dissociated from a patient-derived vestibular schwannoma sample that was cultured for 3 weeks at low magnification (1A) and higher magnification (1B). Using fluorescent markers, we show the presence of schwannoma cells (green) and cell nuclei (blue). These data demonstrate the successful development of a viable model for investigating vestibular schwannoma using patient samples. Patient-derived cell cultures were then exposed to neurotrophic growth factor inhibitors to examine the effects on cell growth and proliferation.

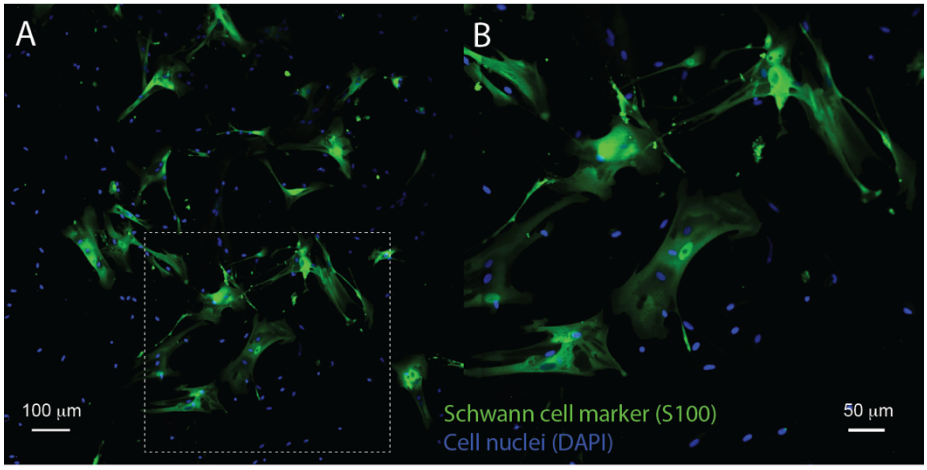

Figure 1. Immunofluorescent labelling of dissociated vestibular schwannoma cells cultured for 3 weeks. *A. shows dissociated and cultured patient-derived schwannoma cells. B. represents the dashed box in A.*

Cells in culture were exposed to four different neurotrophic growth factor inhibitors to examine the effect on schwannoma cell growth and survival. Cultured cells were exposed to inhibitors for 3 days and then cell viability was assessed.

Figure 2 shows cell viability of patient-derived vestibular schwannoma cells following exposure to inhibitors A, B, C, and D. Our experiments show that inhibitor A had a highly significant effect on the viability of patient-derived vestibular schwannoma cells, reducing their viability to 7% (red box). The other inhibitors did not appear to affect cell viability. Inhibitory effects using combinations of drugs (not shown) decreased cell viability only if inhibitor A was included.

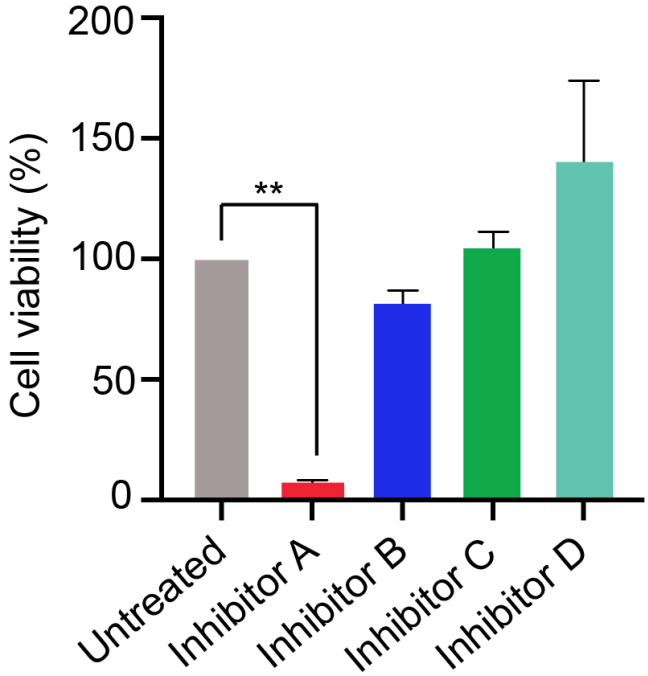

Figure 2. Cell viability after treatment with inhibitors. *Cell viability assay shows a significant decrease in viability of patient-derived schwannoma cells in the presence of inhibitor A (red), p<0.001.*

Unanswered Questions

1. A dose response curve of inhibitor A will determine the optimal dose for slowing and preventing growth of schwannoma cells.
2. The effect of inhibitor A on other cell types of the inner ear will need to be determined to ensure there are no unexpected side effects on cells that may be exposed to this potential treatment.

What do these research outcomes mean?

Our preliminary study examines the effects of neurotrophic growth factor inhibitors on several models of vestibular schwannoma, including those derived from patient samples. We identify one very promising inhibitor that stops growth of cultured schwannoma cells. These very exciting results demonstrate for the first time that targeting and inhibiting neurotrophic growth factors can stop the growth and proliferation of vestibular schwannoma cells. This is the initial step toward a pharmacological intervention and treatment for vestibular schwannoma. Additional studies are needed to optimise treatment dose and identify any potential side-effects in non-tumour cells.

We would like to thank the Brain Foundation and donors that have supported this research.