COMMENT

Comment on ‘Adult skin-derived precursor Schwann cell grafts form growths in the injured spinal cord of Fischer rats’

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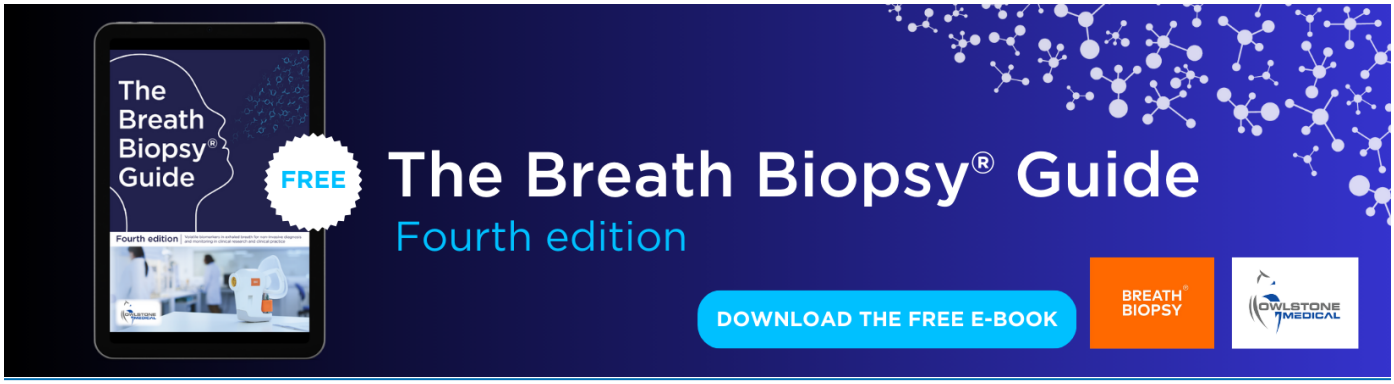

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COMMENT

Comment on 'Adult skin-derived precursor Schwann cell grafts form growths in the injured spinal cord of Fischer rats'

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To the Editor:

May *et al* show that, when grafted in the injured spinal cord, Schwann cell transplants derived in culture from adult skin-derived precursor cells (SKP-SCs) may induce uncontrolled growth of large masses of cells, which the authors suggest are phenotypically reminiscent of Schwannomas [1]. While this study may have worrying implications for the potential use of dermis-derived cells in clinical trials for spinal cord injury (SCI), we would like to suggest that a number of factors impacting such decision should be taken into consideration.

First, the authors acknowledged mycoplasma contamination and concomitant malignant transformation of their SKP-SC cultures as a likely possibility. Any clinical use of SKP-SCs would involve expansion of the cells under good manufacturing practice (GMP)-grade conditions, and thus mycoplasma contamination of the Schwann cells would be extremely unlikely. GMP-grade cell culture, as compared with standard lab procedures, implements extensive protection measures and in process testing precisely to prevent contamination, cell transformation and other unwanted issues [2].

Second, we would like to propose that the original cellular input used by May *et al* should have been derisked by following a relatively simple strategy. This study employed dermal sphere cultures which were passaged twice in floating conditions. However, an important consideration to bear in mind is that this initial cell input was (by definition) diverse. Early passage rodent-derived dermal sphere cultures are highly heterogeneous, and a quick look at the literature would show that they may contain dermal precursor cells [3], melanocytes [4], Schwann cells [5–7], pericytes [5], muscle satellite cells [8, 9], fibroblasts [10], and possibly other cell types and states (e.g. different degrees of differentiation/dedifferentiation or activation). Furthermore, we have previously shown that there is a neurogenic cell subpopulation of $p75NTR^+$ cells in dermal sphere cultures that includes at least two different cell types, Schwann cells and pericytes, which can easily be separated by the differential expression of CD56 [5]. Crucially, no neurogenic activity is detected in spheres depleted of the Schwann cells [6, 7]. Thus, although several authors keep using to this day the so-called skin-derived precursors for neurogenic derivation out of dermal stem cell cultures [11], we would suggest that purifying the neurogenic population at the source material level would significantly reduce the passaging required to purify Schwann cell precursors in meaningful numbers and thus reduce the risk of cell transformation.

Third, the cell masses found in this study were considered to arise from fully differentiated Schwann cells, as defined by the expression of marker p75NTR. This conclusion comes from the fact that the dermal spheres were differentiated onto Schwann cells *in vitro*, transduced for fluorescent tracking with a green fluorescent protein (GFP)-expressing lentiviral vector, further expanded for 5–10 passages (in attachment culture conditions) and then FACS-sorted as $p75NTR^+GFP^+$ cells [1]. However, no reference was made in the study to the purity achieved by their sorting strategy. Although previous studies that used a similar sorting strategy had shown purity of the SKP-SC fraction >95% [12], there is no guarantee that this was the case here. Besides, we have observed that non-neurogenic cells in dermal sphere cultures, which can also be $p75NTR^+$, easily outgrow the Schwann cell precursors when seeded under attachment-promoting conditions (5 and unpublished data). Thus, any purity below 100% may pose a substantial risk of mesenchymal precursor cells being injected as part of the SKP-SC cultures, and these cells might be responsible for some of the cell masses reported in the study.

In conclusion, the study by May *et al* is a useful reminder for researchers willing to translate preclinical, proof-of-concept studies into the clinical arena that protocols must be designed having in mind

that precursor cell purity must be optimized and controlled through exhaustive QC procedures, and that any risky *in vitro* amplification steps which are not undoubtedly needed should be avoided. If these requirements that will improve safety and efficacy of the cell product are met, the use of SKP-SC-based cell transplants in SCI patients remains a scientifically sound approach.

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