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# Promoting engraftment of transplanted neural stem cells/progenitors using biofunctionalised electrospun scaffolds

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ABSTRACT

With the brain's limited capacity for repair, new and innovative approaches are required to promote regeneration. While neural transplantation for a number of neural disease/injuries have been demonstrated, major limitations in the field include poor cell survival and integration. This, in part, is due to the non-conducive environment of the adult brain, failing to provide adequate chemical and physical support for new neurons. Here we examine the capacity of fibrous poly ε-caprolactone (PCL) scaffolds, biofunctionalised with immobilised glial cell-derived neurotrophic factor (GDNF), to influence primary cortical neural stem cells/progenitors *in vitro* and enhance integration of these cells following transplantation into the brain parenchyma. Immobilisation of GDNF was confirmed prior to *in vitro* culturing and at 28 days after implantation into the brain, demonstrating long-term delivery of the protein. *In vitro*, we demonstrate that PCL with immobilised GDNF (iGDNF) significantly enhances cell viability and neural stem cell/progenitor proliferation compared to conventional 2-dimensional cultureware. Upon implantation, PCL scaffolds including iGDNF enhanced the survival, proliferation, migration, and neurite growth of transplanted cortical cells, whilst suppressing inflammatory reactive astroglia.



## 1. Introduction

Development of the central nervous system (CNS) is dependent on a tightly orchestrated sequence of events involving the appropriate temporal and spatial presentation of chemical cues and physical support. These same sequences of events are required to repair the injured CNS, however they are either inhibited or significantly attenuated to an extent that repair is extremely limited. Furthermore, current therapies for the treatment of CNS disease or trauma are non-existent, minimally effective and/or associated with unwanted side effects, thereby highlighting the need for new innovative therapies. In this regard, stem cells, due to their self-renewing and differentiation capacity, have received significant attention for their potential in cell-based therapies. While cell transplantation using stem cells/progenitors has shown promise for a number of neurological conditions, and in some clinical trials (see reviews [1–3]), extensive variability, poor cell survival and insufficient integration/reinnervation remain common limitations impeding their further development. Combined, this highlights the need for the development of technologies to improve the microenvironment for transplanted stem cells and residual endogenous cells in an effort to promote neural repair. In this regard the engineering and functionalisation of biomaterials are of increasing interest.

While numerous biomaterials are available, electrospinning of polymers has drawn attention for neural repair due to the ability to recapitulate the local tissue environment through the manipulation of fiber alignment, diameter and inter-fibre distance. These scaffolds provide physical support for new and residual cells, while also maintaining the architecture at the injury site [4–6]. In particular, a number of studies to date have demonstrated the ability of poly (ε-caprolactone) (PCL) to support neural cells *in vitro* and *in vivo* (see reviews [7–9]). Previously we showed the ability of PCL to support neural stem cells (NSC) *in vitro*, resulting in altered proliferation, differentiation and enhanced neurite growth [10–12].

*Abbreviations:* CNS, central nervous system; CRT, cell replacement therapy; E, embryonic day; ED, ethylene diamine; ELISA, enzyme-linked immunosorbent assay; GDNF, glial-cell derived neurotrophic factor; GFP, green fluorescent protein; iGDNF, immobilised glial derived neurotrophic factor; NSC, neural stem cell; PCL, poly ε-caprolactone; sGDNF, soluble glial derived neurotrophic factor.

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