

● PERSPECTIVE

## Brain repair for Parkinson's disease: is the answer in the matrix?

Two hundred years after James Parkinson first described the cardinal motor symptoms of the disorder that would later bear his name, there is still an irrefutable need for a therapy that targets the underlying pathophysiology of the disease and not solely its symptoms. Parkinson's disease (PD) is classically characterised by Lewy body formation and a relatively selective degeneration of nigrostriatal dopaminergic neurons (Schapira and Jenner, 2011). The loss of dopaminergic neurons from the substantia nigra pars compacta causes a consequential depletion of the neurotransmitter dopamine from the striatum, and it is this loss that causes the motor symptoms experienced by patients. To date, all treatments for this condition are symptomatic in that they simply endeavour to correct the neurochemical and/or electrical anomalies caused by striatal dopaminergic deafferentation in an attempt to improve motor function (LeWitt and Fahn, 2016). While such symptomatic approaches show extraordinary efficacy in the early years after initiating treatment, the underlying disease pathology continues to progress, and eventually their efficacy subsides. In view of this, there remains an urgent need for an alternative treatment approach that is capable of protecting or repairing the brain in order to provide a more sustained benefit to patients.

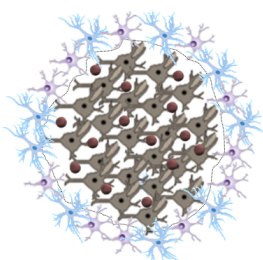
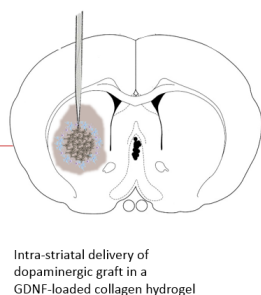
**Brain repair for PD:** Brain repair for PD has developed from a relatively simple conceptual framework - if a primary pathological hallmark of the disease is the degeneration and death of dopaminergic neurons, then it should be possible to replace these neurons with healthy, viable cells. Over the last 30 years, cell replacement therapy for PD has focused on the transplantation of primary dopaminergic neurons sourced from the ventral mesencephalon of fetal donor tissue. A plethora of experimental studies from rodents to non-human primates have illustrated the ability of these cells to survive, integrate with the host system, release dopamine and restore motor function; results that have since translated to clinical trials in PD patients (Barker et al., 2015). However, despite the potential of brain repair for PD, the use of human fetal tissue, obtained from elective abortions, raises many ethical and logistical concerns, which are exacerbated by the extremely poor survival of these cells in the brain post-transplantation (Sortwell et al., 2000). With a survival rate of only 5–10% of implanted cells, there is a requirement for as many as 12 fetal donors per patient which is clearly an impediment to the more widespread roll-out of this approach to patients (Barker et al., 2013). Several factors, occurring at various points of the transplantation process, are thought to contribute to the poor survival of the implanted fetal cells. These include 1) detachment from the extracellular matrix during tissue dissection, 2) growth factor deprivation upon transplantation into the adult striatum, and 3) the host brain's neuroinflammatory response to the implanted cells (Moriarty et al., 2017).

**The potential of biomaterials for brain repair for PD:** Biomaterials - that is, materials that have been specifically engineered to interact with living systems for therapeutic purposes - have the potential to substantially improve brain repair approaches for PD. Structural biomaterials can be used as scaffolds to provide a supportive matrix for transplanted cells, and can be functionalised for delivery of therapeutic molecules that can enhance survival, axonal outgrowth and connectivity of transplanted cells. A vast array of different biomaterials are available, and while their characteristics may render them more suitable for some applications than others, in general, they are highly tuneable scaffolds and can therefore be specifically modified to a therapeutic need (Orive et al., 2009). Naturally-derived biomaterials, such as collagen hydrogels, hold the advantage of being characteristically similar to the body's native tissue, making them highly biocompatible and biodegradable, while also naturally supporting cell adhesion without the need for further chemical alterations which may disrupt the immunogenicity of the scaffold. Collagen is also capable of forming *in situ* gelling (and therefore injectable) hydrogels, thus making it an attractive candidate for improving cell replacement therapies in neurodegenerative disorders such as PD. Furthermore, collagen-derived biomaterials have the benefit of already having clinical approval for a wide variety of applications (Bhat and Kumar, 2013). In theory,

collagen hydrogels have the potential to increase the engraftment of cells by intervening at various points throughout the transplantation process where cell death occurs, such as, 1) providing a supportive matrix environment for cell adhesion, 2) providing a reservoir for localised growth factor delivery, 3) creating a physical barrier between the transplanted cells and the host neuro-immune cells (Figure 1).

**Biomaterials improve brain repair in PD models:** We have recently embarked on a series of studies to determine if the conceptual benefits of biomaterial hydrogels can be realised in experimental studies (Hoban et al., 2013; Newland et al., 2013; Samal et al., 2015; Moriarty et al., 2017). In the first instance, we found a dramatic reduction in the host's immune response to transplanted cells (mesenchymal stem cells or primary dopaminergic neurons) when these are injected into the brain in an *in situ* gelling collagen hydrogel (Hoban et al., 2013; Moriarty et al., 2017). This was manifest through a significant reduction in the recruitment and proliferation of both microglia and astrocytes at the transplantation site. Given that intracerebral transplantation of these cells usually stimulates a substantial host immune response, the collagen hydrogel was clearly capable of shielding the grafted cells by forming a physical barrier between the cells and the host brain's immune cells. However, despite the significant reduction in gliosis at the transplant site, this was not sufficient to improve the survival of either mesenchymal stem cell or primary dopaminergic transplants. We hypothesised that this was due to the lack of trophic support immediately upon transplantation, as this is the critical period where the vast majority of cell death is known to occur. Therefore, we then sought to determine if the collagen hydrogel was capable of providing a growth factor reservoir in the brain by functionalising the gels with the dopaminergic neurotrophin, glial-derived neurotrophic factor (GDNF). Injection of GDNF within the hydrogel resulted in a significantly enhanced acute retention of the trophic factor in the brain when compared with a bolus injection of GDNF (Moriarty et al., 2017). We then hypothesised that the GDNF-functionalised hydrogel could provide implanted cells with the localised trophic support required during the critical period immediately post-transplantation which is lacking during the conventional delivery of ventral mesencephalic tissue alone. Strikingly, when we transplanted primary dopaminergic neurons in the GDNF-functionalised *in situ* gelling collagen hydrogel, we found that cell survival was significantly and substantially (5-fold) enhanced, and that this was associated with a greater extent of striatal reinnervation from the grafted cells which translated to a greater level of functional recovery (Figure 2, Moriarty et al., 2017). Taken together, these data indicate that collagen hydrogels can indeed target multiple points of cell death by providing cells with a supportive environment throughout transplantation that is rich in trophic support and capable of guarding the cells from the hostile host environment.

Consistent with these findings, other research groups have also recently reported the benefits of biomaterial application to cell replacement therapies in PD models. Wang et al. (2016) demonstrated the enhanced survival and re-innervation of transplanted fetal ventral mesencephalon grafts through their encapsulation in a GDNF containing composite scaffold consisting of a xyloglucan hydrogel and electrospun short nanofibers. An interesting addition to this scaffold was the tethering of GDNF to short nanofibers, alongside the presence of soluble GDNF throughout the hydrogel, thus providing long-term GDNF delivery at the graft site and sustained release from the hydrogel. Moreover, since the tethering of GDNF to the short nanofibers alone did not result in improved cell survival or re-innervation, this highlights the importance of GDNF release from the graft core to the surrounding striatum, where it can guide and support neurite outgrowth. Adil et al. (2017) have also recently demonstrated that a hyaluronic acid hydrogel can enhance the survival of, and neurite outgrowth from, encapsulated human embryonic stem cell-derived dopaminergic neurons. This hydrogel was additionally functionalised with extracellular membrane derived ligands, RGD and heparin, in an effort to assist cell attachment and trophic factor binding, respectively. Moreover, this study demonstrated the ability of the functionalised hydrogel to improve the efficacy of dopaminergic neuronal differentiation, with a higher fraction of dopaminergic cells obtained *in vitro*, and an increase in the number of surviving cells during enzymatic cell harvest, a step that is thought to be a major contributing factor to pre-transplantation cell death in stem cell therapies. Encouragingly, this further demonstrates the potential of biomaterial applications in future stem cell-based cell replacement therapies.

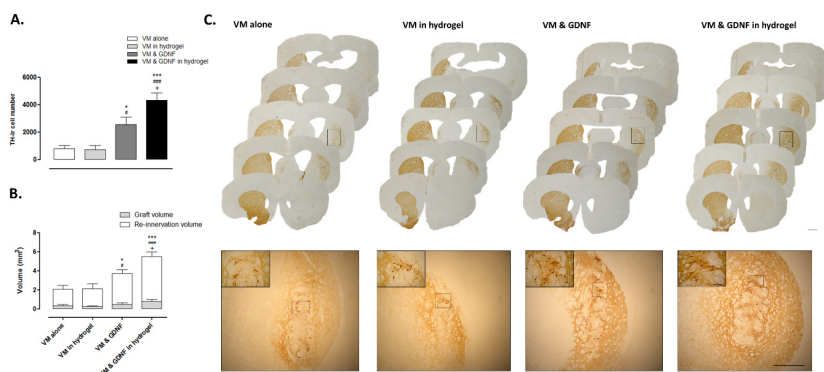


- Supportive environment for cell delivery
- Growth factor reservoir
- Reduced host immune response



**Figure 1** Therapeutic concept of biomaterials for brain repair in Parkinson's disease.

Encapsulation of transplanted dopaminergic neurons in a glial-derived neurotrophic factor (GDNF)-functionalized collagen hydrogel could improve brain repair in Parkinson's disease through a number of different mechanisms. These include provision of 1) a physical scaffold for cell adhesion during intracerebral delivery and engraftment, 2) a local reservoir for GDNF at the implantation site, and 3) a protective barrier against the host immune response.



**Figure 2** Glial-derived neurotrophic factor (GDNF)-functionalized collagen hydrogels improve brain repair in Parkinsonian rats.

Survival of (A) and reinnervation from (B) primary dopaminergic neuron implanted into the hemi-Parkinsonian rat brain (C) is significantly enhanced when they are grafted within a GDNF-functionalised collagen hydrogel. Photomicrographs are of tyrosine hydroxylase immunostained rat brain sections showing dopaminergic neurons. Scale bars represent 1 mm or 100  $\mu$ m (insert). Data are represented as the mean  $\pm$  SEM and were analyzed by one-way analysis of variance with *post-hoc* Bonferroni test. \* $P < 0.05$ , \*\*\* $P < 0.001$ , vs. VM alone; # $P < 0.05$ , ### $P < 0.001$ , vs. VM in hydrogel; + $P < 0.05$ , vs. VM & GDNF. Image from Moriarty et al. (2017).

**The future of biomaterials for brain repair for PD:** It is clear that evidence is mounting that supports the potential of biomaterial scaffolds to enhance brain repair for PD. As cell therapies for PD and other neurodegenerative disorders propel towards the clinic, simultaneously, the area of biomaterial science is also making monumental progress; and the question remains: "is the answer in the matrix?" While further work must be carried out to determine the optimal material for dopaminergic cell replacement therapies, it is indisputable that great potential lies within biomaterial scaffolds and their application to neuroregenerative therapies.

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**Niamh Moriarty, Eilís Dowd\***  
Pharmacology & Therapeutics and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland  
\*Correspondence to: Eilís Dowd, BSc, Ph.D., eilis.dowd@nuigalway.ie.  
orcid: 0000-0002-2668-539X (Eilís Dowd)  
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Reviewer: Sagar Gaikwad, Indian Institute of Advanced Research, India.  
Comments to authors: The perspective article highlights the potential implications of biomaterials for enhancing neuronal repair. In particular, authors discuss the potential use of GDNF-loaded collagen hydrogel scaffolds for the

transplantation of primary dopaminergic neurons to improve the outcome of reparative cell therapies for PD. The article is very interesting, and has its merit and represents a valuable contribution to the literature.

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