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Is there a future for neural grafting? ▲

In a recent issue of *Drug Discovery Today,* Barker and Rosser provide a brief and insightful review on neural grafting in Parkinson's (PD) and Huntington's diseases (HD)[1]. Cell therapies in PD are aimed at replacing lost dopaminergic neurons and are based on extensive data in experimental animals. Following improvement of grafting techniques, transplantation of embryonic tissue in patients with PD has resulted in a clear and long-lasting improvement of 30–50% in motor-performance rating scales[2]. There has also been a progressive reduction or even cessation of medical treatment in open-label trials of these techniques from several centers[2]. By comparison, there is less experimental data on striatal grafts in HD and the few patients grafted so far need to be evaluated longer before any major conclusions are drawn[3].

Recently, the NIH-sponsored, double-blind, placebo (sham surgery)-controlled study on transplants in PD by Freed *et al*.[4] has received a great deal of attention. The study reports that after one year, grafts can provide some symptomatic relief, but only in younger (<60 years) patients compared with sham surgery, although effects are smaller compared with many other studies[2]. Furthermore, 15% of patients developed disabling dystonia and dyskinesias when on little or no anti-Parkinson medication.

Several aspects of this study[4] have raised concern within the neural grafting community: considering that transplanted cells can require many months or even years to mature, a follow-up of one year could be too short for some patients to develop maximal graft-induced effects. In the Freed study, techniques differ from most other studies: donor tissue was cultured for 1–4 weeks before implantation, less tissue was transplanted, a frontal surgical approach was chosen and no immunosuppression was given[2,5]. Freed *et al.* speculate that dyskinesias post-surgery are the result of an excess of dopamine[4], whereas there is no direct evidence to support this idea. In fact, some observations could be seen to directly contradict this proposal[5,6].

It can be strongly questioned whether the study by Freed *et al.* should be

Table 1. Alternatives to the use of embryonic tissue in neural grafting for Parkinson's disease

Cell type	Source	Capacity
Embryonic stem cells	Derived from inner cell mass of blastocyst	Able to develop into all cell types
Neural progenitor cells	Derived from embryonic brains	More restricted regarding their fate
Adult stem cells	Derived from adult brain (ependymal/subependymal zone, hippocampus)	Differentiate into neuronal, glial cell types
Bone marrow stromal cells	Bone marrow	Differentiate into many cell types (e.g. neuronal and glial cells, hepatocytes, myocytes, chondrocytes)
Lipid cells/skin-derived cells	Lipid tissue/skin	Probably multipotent?
Immortalized cell lines	E.g. embryonic ventral mesencephalon	Develop into dopaminergic neurons
Porcine dopaminergic neurons	Porcine embryos	Develop into mature dopaminergic neurons

1359-6446/01/$ – see front matter PII: S1359-6446(01)01934-1

considered to address the full potential of neural grafting in PD. Methodological changes could result in a completely different picture of the therapeutic value of neural grafting in PD and the scientific and clinical communities should be urged to display patience as grafting technology continues to be refined.

The review by Barker and Rosser also describes interesting novel sources of donor tissue that could be of use in transplantation therapy for PD. Different cell types are currently being investigated with the aim of generating as many dopaminergic neurons as possible and thereby making the neural grafting procedure more reproducible and available for a larger number of patients (Table 1).

Exciting research during the coming decade will reveal which cell type is most effective and then this can be applied in multiple centers worldwide as a true therapy for PD.

References

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The broader applications of uHTS ▲

The recent article by Julian Wölcke and Dirk Ullmann[1] in *Drug Discovery Today* describes the growing number and variety of tools available to enable researchers to fully realize the benefits of miniaturized ultra-high-throughput screening (uHTS). The article describes new homogeneous and heterogeneous/no-wash assays, plate types, detection technologies, and advances in robotics and data management. The availability of these new tools undoubtedly assures the increased use of high-density, miniaturized screening in the early phases of drug discovery. This will bring the intended benefit of streamlining the current target-to-lead paradigm of lead discovery. This is crucial to the drug discovery industry as the number of therapeutic targets will increase in coming years, as will the pressure to develop new drugs against these targets in an inexpensive and efficient manner.

As with all new technology, there are unexpected collateral benefits that arise beyond those originally intended. The uHTS technology described in the Wölcke and Ullmann article could have broader applications and influences on the drug discovery process. As the discovery of the genetic basis for disease progresses and the identification of new proteins continues, there are going to be many biological molecules and pathways whose role and function are unknown. An example is orphan G-protein-coupled receptors (oGPCRs) for which there is no known function, but an expected therapeutic role given the frequency that this receptor class plays in disease. uHTS can be a useful tool in investigating these orphan targets. Large collections of small molecules, natural products or peptides can be screened against these receptors after they have been cloned and expressed in test cell lines. Receptor agonists, identified from these screens can be used to explore the function of these receptors and to develop receptor antagonists. In this way, screening can be used, not only in the drug discovery phase, but also in the phase of target discovery. The benefit of uHTS at this point is to keep the cost low, where the likelihood that the target being studied has a high chance of not being useful.

The development of predictive tools for ADME and toxicity has become important to the development of new combinatorial libraries. Computational models can be used to guide the development of libraries with desired properties. To develop these models, one needs chemical and structural information from a set of representative molecules. This information can be obtained by screening large collections of molecules with *in vitro* assays for specific ADME or toxicity properties. Large and diverse libraries of molecules offer a rich source of information for the development of these predicative models. Screening these collections in uHTS format provides a powerful way to develop this information for model building.

These are just two benefits of uHTS technology beyond the original intent of speeding up the traditional targets-to-lead paradigm. The tools described in the Wölcke and Ullmann article will enable researchers to more effectively pursue and realize these benefits. As this new technology works its way into the laboratories of discovery researchers, I am sure we will see that it will change the way drug discovery is pursued in the future.

Reference

1 Wölcke, J. and Ullmann, D. (2001) Miniaturized HTS technologies – uHTS. *Drug Discov. Today* 6, 637–646

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1359-6446/01/$ – see front matter PII: S1359-6446(01)01935-3