Stem cell therapy for brain repair after injury

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Introduction

This submission to the commission focuses on the potential for stem cell treatment for neuronal regeneration after traumatic brain injury (TBI). Certainly within the field of neurosurgery and neurology, moving from disease amelioration towards rebuilding and regenerating has paralleled the advances in knowledge and technology. Stem cells provide promise towards regenerative treatment following a neurological insult. While many stem cell trials have emerged in recent years, the medical community, with close scrutiny for the general public and policy makers, has ensured rigor in bringing these potential therapies to the fore. Particular attention has been made to ensure the focus of study has been on the efficacy, safety, and mechanism of action underlying cell therapy. With relevance to the 'Commission on the Future of Surgery', developing improved systems for delivering therapies directly into the brains of patients with TBI becomes important. This includes the development of innovative mechanisms of delivery of stem to the site of injury and safe effective administration of relevant pharmaceutical therapies. Methods include intravenous and intra-arterial injection, but certainly in the last decade, the notion of stereotactic insertion of novel drug delivery systems and stem cell transplantation directly to the brain by neurosurgeons has become a defined potential sub-specialism at neurosurgical meetings. While it suffices to say that all these cell transplantation therapies are in various experimental phases, with some in advanced clinical trials, no doubt a future neurosurgeon with an interest in cell transplantation, and critically in neuro-regeneration is just a matter of time.

Modern restorative neurosurgery began about 30 years ago when neurosurgeons and neurobiologists envisioned the possibility of replacing degenerating neurons in patients who had diseases including Parkinson's and Huntington's. These trials did not have the desired outcomes and research in this area dwindled until the last decade or so. More recently, our understanding of the neurobiology has led to a refocus on well characterized and defined stem and progenitor cells. They have the potential not only to replace the transmitter which may have been depleted, but also the neuronal circuitry, thus regenerating the nervous system. Several cell types have been transplanted in experimental models, and current trials are investigating a host of cell types in diseases such as Parkinson's disease, Huntington's disease, spinal cord injury, ALS and stroke. Further trials in multiple sclerosis, TBI and cerebral palsy are in the not

too distant future. Examples of current trials include the UK based company Reneuron, which use human fetally derived stem cells that are transplanted into the brain following ischemic stroke. They have completed Phase 1 and 2 clinical studies and are due to launch a Phase 3 clinical trial. Another company, US based Neuralstem, have a fetally derived neural stem cell line, which has been tested for safety in ALS. Further indications are in the pipeline including stroke, TBI and spinal cord injury. The UK Professor Raisman, used olfactory ensheathing cells for spinal cord injury in a first in man operation, generating a large worldwide press response. Further patients to these trials are funded by a UK stem cell foundation.

Certainly many challenges remain for such therapies to emerge as standard treatment. The first challenge is to find one therapy where the efficacy has been proven in a large clinical trial, and therefore becomes a treatment option for the mainstream neurosurgical community. In order to determine this, further evaluation of efficacy and safety are required. Indeed, safety of cells capable of proliferating necessitates the careful monitoring so that these never show any tumour potential. This demands greater regulatory scrutiny as a consequence, and frequent re-evaluation. Moreover, the ethical consideration of using human fetally derived cells for patients presents the medical community with further requirements to be cautious. While public opinion is shifting, a reassuring evolution of the treatment is that as technology and our understanding of stem cells improve, we can reprogramme the patients' own cells, rather than use fetally derived treatment options.

However, the success of the aforementioned studies is hindered by one key limitation. Indeed, poor survival of the graft results in a lack of sustainable recovery after stem cell transplantation. While many drugs hold promise, the presence of the blood-brain-barrier limits effective delivery of pharmacological therapies to ensure long-term survival and regeneration of transplanted stem cells. To this end, pharmaceutical companies have largely focused on chemical transporter technologies. Nonetheless, there has recently been a shift towards the development of brain-friendly hardware/devices to ensure controlled and targeted delivery directly to the site of injury. With decades of involvement in other nervous system drug delivery devices such as morphine and baclofen pumps to treat pain and spasticity, neurosurgeons are well positioned to develop and implant similar devices to ensure the success of stem cell therapy.

While companies begin to manufacture various lines of stem cells in world-class facilities, several questions will be asked for each putative treatment. Firstly, do all the cells maintain the same properties, including genetic material, as they divide. Also, do the cells act by integrating to the human nervous system, or do they act by provide support to their surroundings. Importantly do they benefit the patient, and what is the outcome, including side effects.

Regenerative surgery in 5 years

In 5 years, the likely scenario is an increased number of clinical trials with more and more cell types to refine and rationalize the treatments available. One or more treatments may become mainstream, and once there is a proven treatment that is neurorestorotive, the potential abundance of cellular types and therapies is exponential. Careful attention to clinical outcomes, especially quality of life need to be observed. Along with this is narrowing of the type of cell for cell based therapy. Perhaps 1 treatment on the market with several indications in the pipeline.

10 years and beyond

In the more distant future, combination pharmacotherapies or bioscaffolds with cell transplantation will be directed at further improving the functional outcomes in our patients. Biomaterials would aim to improve the efficacy of stem cells by acting as adjunct treatments. This may include materials such as Hydrogels, for instance, seen in experimental peripheral nerve regeneration. We may be augmenting survival of transplanted cells with infusion of supportive growth factors delivered using implantable drug delivery devices.

Beyond this timescale we can speculate on the use of chip technology, as already trialled by several US institutions, as implants directly upon the nervous system. Certainly, chip technology to activate the nervous system, coupled with cell based therapy and bioscaffolds means that the reality of regenerating the nervous system remains in the realms of possibility. As surgeons, who often defined technological advancement, the idea of being at the forefront of essentially attempting to rebuild and reboot the brain is attractive, especially to those of us who have over 20 years of service to give. Certainly one important aspect is to ensure that we ensure that we bridge the gap between the scientific community and the general public. This would no doubt include training and education programs. While educating the public ensures that we have moral checks and balances, importantly it also ensures that our expectations and hopes are realistic for such complex surgical therapies. Only then can we achieve the goal of neuro-regeneration for patient benefit.