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Regenerative Neurology – The Future

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ABSTRACT

The concept of regenerating the nervous system is not a new one- one hundred years ago, in 1913, Santiago Ramón y Cajal established the central dogma of the emerging field of neuroscience: *"In the adult centres, the nerve paths are something fixed, ended, and immutable."* Cajal himself speculated whether the science of the future would ever be able to reverse this "*harsh decree*". It is the aim of Regenerative Neurology to do so.

Regenerative Medicine aims to replenish or replace damaged or abnormal cells, organs and tissues to establish normal function. Regenerative Neurology is the application of these principles in the context of neurological disease- its application may take many forms, including: implantation-based techniques; "self-repair" therapies and generation of diseased tissue models. These three concepts will likely form the basis of the future of Regenerative Neurology. In this essay the current progress and the trajectories they may follow in the future will be explored.

Key Words: Neurology; Regenerative medicine; Neuroscience

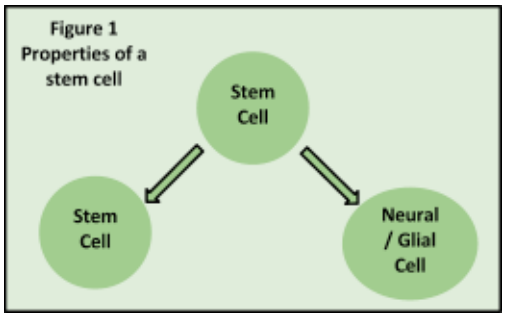
Introduction

The concept of regenerating the nervous system is not a new one- one hundred years ago, in 1913, Santiago Ramón y Cajal established the central dogma of the emerging field of neuroscience: *"In the adult centres, the nerve paths are something fixed, ended, and immutable."*[1] Cajal himself speculated whether the science of the future would ever be able to reverse this "*harsh decree*". It is the aim of Regenerative Neurology to do so.

In time this view was challenged; it has been established that neurogenesis occurs in the Central Nervous System (CNS) of mammals, including humans.[2,3] Constituitive neurogenesis occurs in the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate nucleus of the hippocampus. Neurogenesis has been shown to occur in other areas of the CNS after pathological stimulation.[3] Oligodendrocyte Precursor Cells (OPCs) are capable of diferentiation into Oligodendrocytes in response to demyelination.[4]

Regenerative Medicine aims to replenish or replace damaged or abnormal cells, organs and tissues to establish normal function.[5] Regenerative Neurology is the application of these principles in the context of neurological disease- its application may take many forms, including: implantation-based techniques; "self-repair" therapies and generation of diseased tissue models.[6,7] These three concepts will likely form the basis of the future of Regenerative Neurology. In this essay the current progress and the trajectories they may follow in the future will be explored.

Stem cells are central to the approaches described above. They are defined by their capacity for self-renewal and differentiation into specialised cell types (Figure 1). Many types have potential as therapeutic options in neurological disease.[8] Among these are Embryonic Stem Cells (ESCs), derived from the blastocyst; induced Pluripotent Stem Cells (iPSC), genetically reprogrammed from adult cells and adult Neural Stem Cells (NSCs), endogenous populations of stem cells able to differentiate into neural and glial cells, as mentioned above.[9-10]



Stem Cell Transplant Therapy

Some diseases of the nervous system may be good candidates for stem cell implantation therapies. For example, Multiple Sclerosis involves the loss of one cell type, the myelin-producing Oligodendrocyte. This condition characterises a disease particularly amenable to stem cell treatment: loss of a *single* population of cells underlies its pathogenesis.[11]

This principle of replacing these Oligodendrocytes has in fact been tested, and early research has yielded encouraging observations. Human ESCs and NSCs implanted into a mouse model of hypomyelination showed functional remyelination.[12-13] Recent work by Wang et al achieved remyelination in this mouse model by implanting Oligodendrocyte Progenitor cells, themselves derived from human iPSCs (hiPSCs).[14]

Multiple Sclerosis is one example, but various other diseases in the CNS involve loss of only Oligodendrocytes.[15] Many others have a different monocellular origin, such as Parkinson's and Huntington's diseases.[8]

The Dopaminergic neurons (DN) lost in Parkinson's have been generated from mouse ESCs, which on transplantation have shown to be functional in an animal model of the disease.[16] DNs have also be generated from mouse and human iPSCs.[17-18] On transplantation of the mouse iPSCs in a rat model of Parkinson's, there was clinical improvement.[18] hiPSCs from Parkinson's patients have been differentiated into DN and transplanted into Parkinsonian

rodents, showing a small functional effect.[19] The above studies and others constitute growing preclinical evidence for the potential efficacy of stem cell transplants.[12-14,16-20]

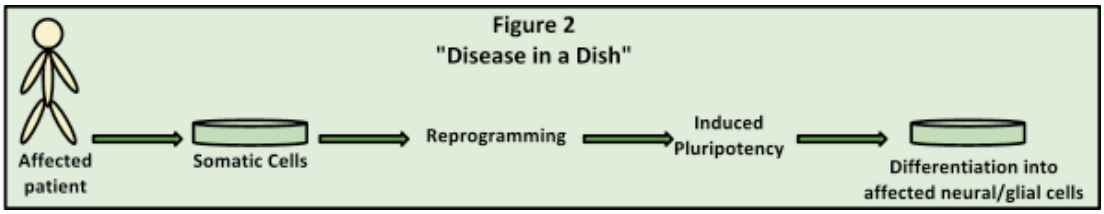
Stem cells unfortunately share one of their central properties, the ability to self-renew, with another type of cell: cancer cells.[21] This other side of the double-edged sword of the so-called "stemness" of stem cells could lead to tumour formation in transplant patients and hinder attempts to bring these treatments to the clinic.[8,22] *Primum non nocere* (first, do no harm), one of the fundamental principles of medicine, renders it pertinent to evaluate this risk of tumourigenesis.

It has been suggested that the *ex vivo* treatment of stem cells may influence their potential to form tumours.[8] Wang et al's recent work has shown mice receiving stem cell transplants in their study had not developed tumours at a 9-month follow up.[14] They identified their differentiation protocol as eliminating the potential of the cell population to form tumours; mice engrafted with cells from an early protocol stage formed tumours. A study of undifferentiated ESCs in a rat model of Parkinson's disease suggests that the level of differentiation of engrafted cells does have an effect on the risk of tumour formation.[23] Immunogenicity has also been a concern of researchers in this area, but recent work has established that both ESCs and iPSCs have little impact on the immune system of transplant hosts.[24-25] Virus-free iPSC reprogramming techniques have also brought this approach a step closer to the clinic.[8]

This research demonstrates the potential of stem cell transplantation techniques. Given the ethical concerns regarding ESCs and limited availability of NSCs, it seems likely that future research will focus more and more on iPSCs.[8] Research should continue to progress to human studies, primarily regarding the safety of transplanted cell populations and developing safe differentiation protocol. Observations of the first iPSC trials in humans are eagerly awaited.

Disease Modelling and Drug Discovery

Another of the exciting prospects of Regenerative Neurology is the use of iPSCs to develop *in vitro* models of disease, both to study their pathogenesis and screen possible therapies (Figure 2). This "disease in a dish" approach is appealing, given the lack of readily available neural tissue samples and the limitations of animal models.[26-27]



Again, the principles of this method have been shown to be feasible, justifying future efforts to refine the field- many disease specific stem cell populations have been generated from patients.[28-30] Recent work in a Motor Neuron Disease (MND) model, derived from hiPSCs

(acquired from a MND patient), has provided a unique insight into the pathogenesis of this disease.[31]

This "disease in a dish" approach may also be able to provide models for drug screening, wherein therapeutic candidates can be tested on an *in vitro* model of neurological disease. Studies in such a model of Alzheimer's Disease have elucidated different drug responsiveness in different kinds of the disease.[32] Similar work has shown that neurons at different stages of differentiation may react to drugs differently, highlighting the need for tight standardisation of differentiation protocol if these methods are to precede clinical application.[33]

Work into screening for drugs is in its very early stages, and it is not yet clear how accurately *in vitro* models will predict *in vivo* reaction to drugs- this should be balanced against the poor predictive value of animal models in clinical translation.[34] Additionally, the complexity of some diseases, such as Autism, thought to originate from altered cortical layering, is beyond current technology.[19] Continuing validation and advancement of this technology may yield sufficient evidence to cement iPSC-based disease models firmly into the repertoire of both those investigating neurological disease and conducting preclinical drug trials.

Utilizing endogenous stem cell populations

The endogenous stem cell population in the CNS consists of NPCs with the ability to give rise to neurogenesis and gliogenesis, found in discrete areas (see above), and, to a lesser extent, diffusely in the CNS.[3] These populations have been shown to proliferate in response to pathogenic situations, such as stroke, in rats.[36] Cells arising from this induced proliferation have shown migration towards the ischaemic boundary in stroke.[37-38] Researchers aim to capitalise on this intrinsic ability of the CNS and facilitate functional healing.

This approach circumvents the ethical issues regarding the use of ESCs, and the difficulty of establishing safe iPSC lines for transplantation.[39] However, recognition of the *in vivo* incapacity of the CNS to facilitate complete and functional repair has led some to think the complex neural environment cannot be regenerated in this way.[40]

Conclusion

Regenerative Neurology is a complex field, the full scope of which surpasses this essay. I include those areas that may well comprise the future of this field, using illustrative examples throughout, focusing mainly on the CNS. These principles may also be applicable in the Peripheral Nervous System.

The ultimate aim is the application of these principles in medicine, and the alleviation of the suffering of many millions of patients. Neurologists currently manage many diseases with no cure; patient need is the driving force of this research and motivates the evolution of Regenerative Neurology into a clinical science.

iPSCs may offer the greatest potential for facilitating this- research should make them

increasingly safe and efficient, and advances in both disease modelling and stem cell transplants will complement each other. This research should run in parallel to the study of endogenous stem cells to elucidate the complex *in vivo* neural environment. Cajal would scarcely believe what has been achieved since 1913. Now, in 2013, I cannot help but wonder what the next 100 years of Regenerative Neurology research will yield.

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