Stem Cells and Parkinson's Disease: The Facts

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Stem cells and their potential for the treatment of a wide variety of medical conditions, including Parkinson's disease (PD), are often in the news. Yet many people are unsure what the term "stem cell" refers to, nor whether stem cells might offer new treatment methods for PD. In this brief article we will describe in simple terms what constitutes a stem cell and the potential of stem cells for new PD treatments.

What is a stem cell?

Stem cells can best be thought of as a type of immature "template" or unspecialised cell (similar to a blank artist's canvas). A stem cell has two important properties; firstly it has the ability to divide itself into two identical cells many times over, thus reproducing identical copies of itself. Secondly, a stem cell can also divide to produce one or two more mature cells (known as progenitor cells), which, under the right conditions, can develop into a neuron or other brain cell, or into a cell in another part of the body (see Figure 1). The division and development of stem cells is crucial for the normal growth and development of the brain and the body in babies and young children, but as the child grows to adulthood stem cells gradually become less numerous in most parts of the body. Nevertheless, even in adult life, stem cells can still be found in some organs, such as the intestine, where they are responsible for the continual replacement of the gut lining throughout the entire life span. Since this article is only concerned with the role of stem cells in the brain, we will restrict our discussion to stem cells in the brain.

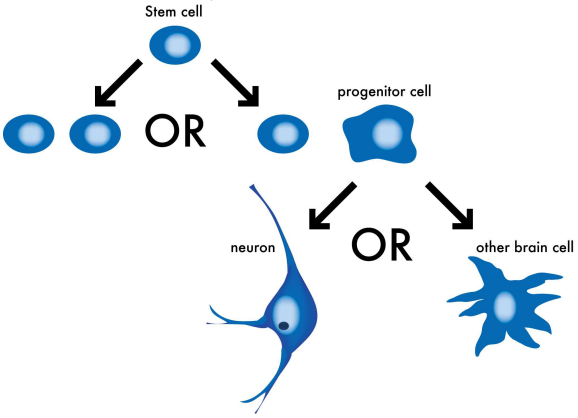

Figure 1: A stem cell can either produce two identical copies of itself, or one or more progenitor cells. A progenitor cell is a slightly more developed cell that is no longer a stem cell, and can develop into a variety of mature cell types.

Figure by Heidi Cartwright

Where are stem cells found in the adult brain?

For most of the last century it was believed that brain cells (neurons) in the adult could not reproduce themselves, and therefore were not able to be replaced. In 1998 researchers were able to demonstrate that the adult human brain contains a small number of stem cells which are able to divide, thus giving birth to new brain cells. This process is known as *neurogenesis*. Rather than occurring throughout the brain, however, neurogenesis appears to occur only in two specialised areas of the brain, a narrow border of tissue on the edge of the caudate called the *subventricular zone* (SVZ), and also in a small area called the *dentate gyrus* within the brain's memory area, the hippocampus. Astonishingly, some of these new brain cells don't remain in the place of their birth but

have the ability to move to other regions of the brain where they develop into cells with specialised functions. So, for example, in the adult rat, brain cells born in the SVZ move a considerable distance along a special pathway to an area of the brain important for the detection of odours. A similar migration process also occurs in the olfactory system in the human brain.

What might stem cells offer People with Parkinson's (PWP) disease?

As the symptoms of PD are caused by the death of brain cells that produce the chemical dopamine, researchers have suggested that stem cells might be coaxed into developing into new dopamine-producing neurons which could replace those dying in the PD brain. There are two ways this might be done. Firstly, stem cells in the brain might be encouraged to reproduce in greater numbers and to travel to the pertinent areas of the PD brain where they would be encouraged to develop specifically into mature dopamine-producing neurons. This would likely be achieved by manipulating the chemical environment of stem cells to encourage them to multiply, to migrate within the brain and to develop into dopamine cells. Secondly, stem cells could be used to produce new dopamine cells outside the body harvested from human embryo's or from a variety of body tissues during life, such as from the umbilical cord or the nose. Recently it has also become possible to produce stem cells in a laboratory by genetically manipulating other body cells, such as skin cells. Stem cells from any of these sources would then be multiplied and grown into dopamine-producing neurons within a laboratory, before being surgically reintroduced back into the brain. Either of these approaches would aim to replace brain cells dying in PD with new dopamine-producing cells, thus increasing the amount of dopamine in the brain's motor circuits and restoring normal movement.

What are the hurdles in achieving such treatments?

Like the brain, the biology of stem cells is very complex and we are in our infancy in understanding these cells. We need to understand how stem cells are born, how they move, how they develop and how they are regulated. To ensure that any therapy for PD based on stem cells will be safe and effective we need to achieve a much greater understanding of all these processes than we have to date, and this is likely to take some years to achieve. While one of the current problems with experimental transplantation of cells into the brain in animal models is often the low survival rate of the cells, it is also important to ensure that the cells do not survive and divide *too* well, as uncontrolled cell division can result in brain cancer, another common problem in these experiments. In the 1970's, long before stem cells were discovered in the human adult brain, dopamine-producing neurons harvested from the brains of human embryos were transplanted into the brains of a number of patients with PD. These early attempts at a "restorative" therapy have given us some further clues regarding the benefits and problems associated with the introduction of dopamine cells into the human brain. While some patients enjoyed a reduction in their PD symptoms following the surgery, a considerable proportion also developed uncontrollable movements (dyskinesias) after transplantation, a side-effect attributed to the inability to control how much dopamine the new cells produced. This unforseen complication, together with the considerable ethical and practical issues surrounding the use of human embryos for this therapy, eventually lead to

the abandoning of this approach. More recent analyses of the brains of several of these transplantation patients who have subsequently died revealed other unexpected phenomena. We do not yet have a complete understanding of how a brain cell knows it is supposed to be a brain cell – or more specifically a dopamine-producing cell. Clearly, just being in the brain does not necessarily result in an immature cell developing into a brain cell, as in the early transplantation trials some of the transplanted brain cells were found to have developed into other cell types in the brain, such as bone or hair. Another important factor to be considered is the fact that dopamine itself is known to control new cell birth in babies and children. It is likely therefore that dopamine is an important regulatory factor for stem cells in the adult brain, but we know little about how this works, nor do we know how PD, a disorder in which brain levels of dopamine are significantly reduced, affects new cell birth. We also need to understand the effects of dopamine-based anti-parkinsonian medication on new cell birth in the PD brain.* Of course the replacement of brain cells can only reduce the symptoms of PD but does not cure the disorder, which would still progress within the brain. This is relevant as it appears that newly transplanted brain cells are not immune to the effects of PD, as several recent reports describe transplanted embryonic cells developing Lewy bodies, abnormal accumulations of protein characteristic of the PD brain. This suggests that newly born, or transplanted, stem cells, while possibly offering a temporary improvement in motor function, may also be eventually damaged by the progressive nature of PD. Even if this is the case, it is hoped that stem cell-based therapies may one day be able to provide effective relief from PD symptoms for time periods measured in years, rather than the hours currently provided by most anti-parkinsonian drugs.

How close are researchers to trying stem cell-based treatments in PWP?

Stem cell transplants are already being successfully used in the clinic to treat spinal lesions and in leukaemia, where stem cells are replaced during stem cell-containing bone marrow transplants. These treatments demonstrate the potential of stem cells and intensive research is being performed all over the world to improve our understanding of stem cells and how these can be used therapeutically for PD. Research has progressed to a point where stem cell-based approaches are being used in experimental models of PD in monkeys, usually the last step before promising approaches are tried, albeit cautiously, in a small number of human subjects. As we write, however, human trials of stem-cell based treatments have not been attempted nor published in the medical literature. As a result, no stem cell-based treatments for PD patients have been approved by the Australian Therapeutic Goods Administration, which monitors the safety and efficacy of medical treatments in this country, nor by any similar organization in any other major Western countries. While Parkinson's NSW is aware that some such "treatments" are being advertised, unproven and at great cost, via overseas-based websites which can be accessed in Australia, we do not recognise or recommend these approaches. While the slow progress of research is frustrating (also to those of us who do it!) past experience has taught us that this is an area where caution – and knowledge - is advisable. Like many other researchers, patients and their families we too hope that one day stem cells might provide new, more effective PD treatments, but let's do the research first.

*The effects of aging, PD and PD medications on stem cells are currently being investigated by the authors and their colleagues.