The Possible Future Applications for Embryonic Stem Cells in the Treatment of Neurological Conditions

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Stem cells are revolutionising the medical landscape and the wider world. The way in which they have been viewed by us has transformed in the last 100 years from their discovery to practical application in hospitals around the world. A backlash of medical and ethical controversy has caused a politically directed drive of research rather than a scientific one, perhaps unjustly. However, there is no doubting the potential for this exciting new field of medicine.

Stem cells are a relatively new and fascinating branch of scientific research into new medical treatments. Our paper shows how stem cells can be applied to a few neurological diseases including Motor Neurone Disease, Alzheimer’s disease and sensory system disorders. Significant research into these diseases is already underway including a research project undertaken by leading professors in stem cell research for MND in 2010: Prof Siddharthan Chandran and Prof Sir Ian Wilmut from the University of Edinburgh; Prof Christopher Shaw from King’s College London and Prof Tom Maniatis of Columbia University New York. The research programme was aimed to use stem cells to study what the precise cause of MND is.

Stem cell treatment has been around for over thirty years now, being used to treat cancer patients with leukaemia for example. Stem cells can be found in bone marrow and from here can be extracted from a healthy person to the cancer patient and can be used to replace blood cells eradicated by the high doses of chemotherapy or radiotherapy that directly work to inhibit or kill the harmful tumour.

With neurological diseases, stem cells can especially be used for regeneration of certain brain cells. Especially when a patient suffers from a stroke and a part of the brain is starved of oxygen, stem cells can be used to regenerate these brain cells that were killed as a result of the lack of oxygen from the stroke. In Alzheimer’s Disease, where the brain cells become degenerate, stem cells can be used to re-grow the degenerating tissue and hopefully in the future to such an extent that Alzheimer’s Disease is eradicated. Stem cells can also work in other ways to treat neurological conditions. In Motor Neurone Disease, stem cells are being used to grow diseases neurones in the lab outside of the body so that these neurones can be extensively studied to find the root cause of MND. Stem cells can further be used to treat the disease, for example if its proven it is in fact the degeneration of glial cells in neurones are the cause of MND, stem cells can be used to regrow these glial cells and so the motor neurones will not just simply waste away.

Stem cells are a very exciting prospect for medicine because they show a way forward into treating conditions that have been extremely challenging to combat before. The ability of pluripotent stem cells being able to differentiate into a vast amount of different cells can be so useful in our future treatments of disease. There are so many diseases that doctors and scientists have to tackle day in day out and stem cell therapy could be a major breakthrough, not only for cancer treatment, but for neurological diseases, brain damage, deafness, blindness and vision impairment, diabetes, wound healing and even baldness. The potential for stem cell therapy is literally endless and it is this range of treatment that stem cells can help to treat these diseases and alleviate suffering for so many people.
Stem cells provide a very realistic way of treating what was previously thought to be chronic neurological conditions. Due to the nature of nerve cells being unable to divide once differentiated from neural stem cells (NSCs), it was considered a long term theory that the nervous system was unable to regenerate. However, an opposition to the theory was first postulated by the American neurobiologist Joseph Altman at the Massachusetts Institute of technology in the 1960s that adult neurogenesis did indeed exist; he had found evidence for its existence through the process of perfecting the complex 3H-thymidine autoradiographic technique. However, despite being published in the scientific journal *Nature* in 1962 it was largely overlooked by the scientific community until the late 1990s, where a renewed interest in the subject directed more widespread and consistent research.

NSCs are the stem cells that are responsible for the phenotypes of the nervous system. They have a degree of multipotency, being able to differentiate into the cells that make up the nervous system. This is the main difference between NSCs and Embryonic Stem Cells (ESCs), as the latter is said to be pluripotent, which is the ability to differentiate into any adult cell type. NSCs do not have this potency. It should be noted that ESCs cannot themselves form an adult organism alone, as they lack the ability to contribute to an extraembryonic tissue (ie the placenta); cells that have this ability (such as the zygote) are said to be totipotent.

ESCs have the ability to differentiate into NSCs given the right culture, which could be seen as an option for the proliferation of NSCs. However, the ethical controversy that surrounds the use of ESCs (derived due to the deliberate termination of early embryos) has resulted in a shift in the direction of research away from ESCs and towards other stem cells. Induced Pluripotent Stem Cells (iPSCs) are created from an adult somatic cell and are induced to regain their pluripotency due to the forced expression of certain genes. They are considered a viable alternative to ESCs as they have been seen to produce similar levels of plasticity as ES cells without having to combat both the ethical issues of discarding embryos and the medicinal issue of Graft Versus Host Disease; the iPSCs can be obtained from the somatic cells of the patient needing a transplant, so the body would not regard the new tissue created by iPSCs as foreign because the new tissue will have the same unique cell surface glycocalx, thus will be recognised as the patient's own.

The general consensus among the scientific community is that neurogenesis continues throughout adult life in two main areas: the Subventricular Zone (situated throughout the lateral walls of the lateral ventricles) and the Subgranular Zone of the Hippocampus. It is in these two areas that a great amount of NCSs are present, thus would be the areas from which NSCs could be extracted from a patient. However, both of these are located in the centre of the brain, so extraction would be an extremely difficult procedure to carry out without causing damage to the brain. Isolation of NSCs is achieved through many ways by the application of a labeling strategy of proteins unique to the NSC such as the marker prominin-1. Once isolated, they can be stimulated *in vitro* by mitogens such as Epidermal Growth Factor and Fibroblast Growth Factor to induce stem cell growth into a wide variety of neurons, astrocytes and oligodendrocytes.

Alzheimer’s is one of the most common forms of dementia in today's society, with over 450,000 people affected just in the UK, and an estimated 26 million affected worldwide. This is the equivalent of about 1 in 85 people and each year that number is growing.
It is considered, like other forms of dementia, to be an age related disorder and so it is most commonly diagnosed in patients over the age of 65. However, dementia in varying forms can affect many people under the age of 65, and there are estimated to be over 16,000 young people affected by dementia in the UK, and this is thought to be an underestimate. It is a physical disorder which affects the workings of the brain and is a progressive disease, meaning the over time, the symptoms get worse, and in some cases, the changes can be quite sudden. Symptoms of AD can include confusion, amnesia, forgetting names, places and recent events, severe mood swings and communication problems. These symptoms are similar to many forms of dementia, and so many people who are not aware of the differences can treat patients with different disorders the same. This can result in massive errors due to the wrong treatment or care being given. However, due to modern diagnostic techniques, the likelihood of being wrongly treated by a qualified professional is very small indeed.

Although the treatment for such disorders has been improved greatly in the past decades, there has been no cure found so far, and so any care is palliative, and is only to try to achieve the best quality of life possible. Despite this, sufferers can find themselves cut off from friends and family by a communication barrier caused by the illness, and also partially by the stigma that is attached to many disorders linked to dementia. Therefore, if any solution could establish a potential cure for such diseases, including Alzheimer’s, then I believe it should be investigated.

Many separate companies and scientists are attempting to unlock more secrets of the disease, but even now, with over 1000 clinical trials having taken place just to try and find ways of fighting the disease, its cause and progression is not understood in great detail. It is however linked with plaques and tangles in the brain.

A plaque is a small deposit of an insoluble protein called amyloid between the brain cells in the grey matter and a tangle is a similar type of deposit but with a different insoluble protein called tau which forms microtubules which coil up on one another. Whereas the tangles are believed to have beneficial and harmful properties, the senile plaques are known to be toxic to the brain cells. These both contribute over the course of the disease to slowly kill off brain cells to result in a brain scan showing a brain with a very different structure, as shown below (Figure 1).

![Figure 1](image_url)
As there is no drug-based treatment available to grow back these lost cells, a lot of research has been done into the application of stem cells into the brain to regenerate lost tissue.

After millions of dollars being spent in the hope of easily producing stem cells without the ensuing ethical arguments about the destruction of embryos in order to harvest ESCs, two teams of scientists in Japan and in the US both succeeded in converting an adult skin cell into a cell which was similar to an embryonic stem cell. This was done through using a cocktail of different drugs which reverted the cells into a previous state.

These ethically derived cells have been shown to be able to develop into fully functional neurons in aged rats’ brains. These cells also significantly improved the rats’ cognitive functions and so the experiment was a success.

This type of experiment could in the future be applied to Alzheimer’s disease in the form of a treatment to regenerate lost brain tissue which results from the plaque deposits and tangled proteins. This would simply re-grow the neurons which had died, meaning that while the disease itself was still present in the brain, the cognitive debilitation resulting from it would be dramatically reduced. However, this would require a very advanced technique of introducing the stem cells into the brain tissue, for example in the temporal lobe or cerebral cortex, where many cells are lost or damaged, which could feasibly be done via open surgery, but by the time that this treatment may be available, keyhole brain surgery may be quite a common operation. Alternatively, the cells may be delivered to the brain via a simple injection, if by then the problem of the blood-brain barrier has been more explored. This potential treatment requires a huge amount more research than what has already been done, as, even now, very little is known about how each neuron in the brain combines to give humans a consciousness and a personality, and so no risks should be taken until more is understood about the functions of groups of neurons.

A further possibility is not to treat the effects of the illness, but to attempt to treat the cause. The plaques and neurofibrillary tangles must be produced by a cell in order to be present in the brain, and so if this is true, then the production of these substances in the cells could possibly be controlled, either by drugs which could affect the cells’ inner workings, by perhaps limiting the functions of the ribosomes producing the proteins, or by removing faulty cells and replacing them. These cells, having specific functions, would have to be replaced by cells producing “safe” levels of amyloid proteins. These replacements could be stem cells which had been induced to differentiate into healthy replicas, and could be introduced using methods similar to those mentioned above, through surgery or a simple injection. However, as stated earlier, at present the only treatment for Alzheimer’s disease is for the symptoms, so this may still only be a very distant possibility.

A disease that can use stem cells to successfully help cure it is Motor Neurone Disease (MND). This is a horrible disease that results in the breakdown of motor neurones that control our movement of muscles and so daily activities become impossible, such as walking, speaking, swallowing and even breathing. Stem cell research so far has played a huge part for scientists studying MND and deciding on a cure for it. The real cause of MND is
unclear and in patients with MND a huge range of factors that could cause the disease are present: for example, mutated genes, blockage in the neurone itself by proteins called aggregates, defective glial cells (which provide support and nutrients for the neurone) and a lack of antioxidants being produced by the neurone causes an increase in toxicity. To fully understand MND scientists have used stem cells in the laboratory to grow motor neurone cells. Having cultured the diseased neurone in a petri dish, the neurone can be extensively studied so as to isolate the factors that cause the disease and also by trialling treatments that work to correct or improve the neurone. Then this work can be used on humans with the disease make sure these causes are eliminated and so motor neurone disease can cease to exist in the world.

A research programme was undertaken in 2010 by four leading researchers: Prof Siddharthan Chandran and Prof Sir Ian Wilmut from the University of Edinburgh; Prof Christopher Shaw from King's College London and Prof Tom Maniatis of Columbia University New York. The research programme was aimed to use stem cells to study what the precise cause of motor neurone disease is and how we can act to prevent this. Skin cells taken from donors were induced to become iPSCs and these can be then further induced to become motor neurone cells which become degenerated in motor neurone disease.

There are many factors found in the neurones that could potentially all be causing the breakdown of the motor neurone. A simple cure could be to insert an iPSC having programmed it to become a specific neurone and have this new motor neurone replace the damaged neurone. While this may seem simple at face value, there are massive complications including the fact that the neurone only grows at 1-3 mm a day and if this damaged motor neurone is reaching from the spinal cord to the tips of the finger, it can take years to grow this neurone to make successful connections with the muscles and the central nervous system. While not totally impossible, this idea would need much more refining including using growth hormones to stimulate quicker growth of the neurone whilst not affecting other cells in the body which again would be massively complicated. Another treatment that could be focused on is to treat the defective supporting glial cells using stem cells. Defective glial cells are very common with MND sufferers and this could either suggest glial cells contribute to MND or that defective glial cells are a side effect of MND. Research would need to be undertaken to study in depth the role of glial cells during the stages of MND and the impact on the defective glial cells upon the motor neurone. If it could be found out that it was in fact faulty glial cells that caused the breakdown in motor neurones, using iPSCs, having programmed them to differentiate into healthy glial cells, could be used to stop the breakdown of the motor neurones. However, it is more probable that the breakdown of neurones is down to a larger collection of factors and that faulty glial cells are only one of the explanatory factors. In this case, stem cells could still be used to replace these glial cells and slow down the effect of the overall disease and this could lead to a healthier longer life for the MND sufferer.

A possible use for stem cells is in the treatment of some sensory system disorders. I believe that this is an overlooked area for the medical use for stem cells, perhaps because chronic sensory system disorders may not carry the same order of severity as, for example, MND. However, this does not give reason for this potential use to become overlooked, as it has the potential to drastically increase the quality of a patient's life if procedures are successful. The reason I believe that this is an exciting field for stem cell cure is that sensory
disorders often result from a small subset of neurons in the sensory organ. This combined with other reasons that will be discussed below present a much less complex solution to a neurological disorder that encompasses many parts of the CNS (such as Alzheimer’s), thus could theoretically be a lot closer to clinical use. (That is if a similar amount or resource was invested into this field.)

Take the eye, for example. Many forms of blindness are to do with Retinopathy, involving the malfunction or loss of photoreceptors at the back of the retina. The other areas of the signal transduction pathway such as the optic nerve have a high probability of being left intact, thus would not need to be repaired if sight is to be restored. Moreover, the photoreceptor is electrically ‘wired’ to the optic nerve at one end rather than two (or more). This adds great simplicity compared to neurons in the brain which need restoring during degenerative diseases such as Parkinson’s, which require a complex system of connections if they are to function effectively. It can therefore be deduced that the problem of creating the right connections in the right place is somewhat easier, as there are fewer connections to be made.

The applications of stem cells into not only extremely intricate neurological disorders, but into all parts of the medical profession have been dreamed of since they were first discovered. While many of these dreams remain unfulfilled, a promising few are on the horizon. As discussed above, these applications of stem cells are neither simple nor quick and even when the treatments are available, they will be able to be improved upon by next generation’s scientists and doctors. Incredible advances have been made, especially recently with the introduction of the iPSC’s, which was a feat no one thought was possible in any animal until a group of men and women were curious enough to try. Ultimately any advances we make are down to the commitment and dedication of our scientists to explore the possibilities that arise. Many examples of this are shown above, such as the previous research that has been done into stem cell treatments for Alzheimer’s, which could inspire a new generation of scientists to attempt the potential treatments laid out above. It also takes a very forward thinking approach to consider the use of stem cells on cases such as blindness, because with such common, chronic conditions they can be sidelined in order to focus on “fashionable” diseases such as MND or Alzheimer’s. In general, many conclusions can be drawn, but not least among them is the fact that while there are so many dazzling therapies and opportunities out there, budding new scientists are a necessity if some of these possibilities are ever to be explored and hopefully unlocked.
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