Perceiving Parkinson's

Cell Transplant Therapies (Day 94)

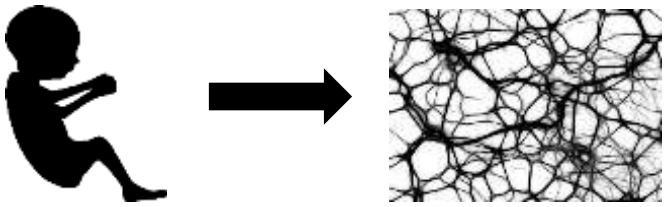
Researchers have been experimenting with **cell transplant therapies** in people with Parkinson's for 20 years, therapies in which **dopaminergic cells** (differentiated cells that release dopamine) or **stem cells** (undifferentiated cells that become dopaminergic cells) from a donor source are transplanted into the basal nuclei of a person with Parkinson's. Many researchers are enthusiastic that cell transplant therapies might one day cure Parkinson's.

These hopes are not realistic, for two reasons. First, Parkinson's is **a disease of neurons, not brain**; dopaminergic neurons throughout the body, including the autonomic and enteric nervous systems, are also affected. They cannot all be replaced. Second, Parkinson's also **damages non-dopaminergic neurons**, such as the memory-storing neurons of the brain's neocortex. These neurons cannot be replaced; if they were, the unique memories that make a person who they are would be lost.

Yet research into cell transplant therapies continues, so let's have a closer look. They may be classified by **donor source** (the source of transplanted cells) into fetal, embryonic, and adult donor sources.

Fetal Donor Sources - Fetal Dopaminergic Neurons

These therapies involve the transfer of **fetal dopaminergic neurons** from aborted fetal brain tissue into a recipient brain, in the hopes that they will continue to release dopamine in the recipient.



Fetal dopaminergic neurons are harvested from aborted fetal brain tissue.

Fetal dopaminergic neurons have been tested in **animal studies** since 1980, when it was demonstrated that transplanting both rodent and human fetal dopaminergic neurons into the brains of "Parkinson's rats" **improved motor defects** in the rats.

In 1987, the first human **uncontrolled studies** involving fetal dopaminergic neuron transplants commenced in Lund, Sweden. Over the next ten years or so, 17 people with Parkinson's received fetal dopaminergic neurons, with each person receiving brain tissue from several fetuses. The results were **variable**, but some participants managed to stop their dopaminergic medications. Similar studies were performed in other countries in Europe and North America, also with variable results.

In 2001, the first human **randomized controlled study** was done, in which 40 people with Parkinson's received either a fetal dopaminergic neuron transplant or sham surgery. By one year, the transplant group **felt no better** than the sham group. Moreover, **15%** of the transplanted participants developed graft-induced dyskinesias that persisted even when their dopaminergic medications were stopped; in some cases, the dyskinesias were so severe that deep brain stimulation was needed to control them.

In 2003, a second human **randomized controlled study** was done, in which 34 people with Parkinson's received either a fetal dopaminergic neuron transplant or sham surgery. By two years, there was **no difference in motor symptoms** between each group. Moreover, **56%** of the transplanted participants developed graft-induced dyskinesias. There was one ray of light to this second study, which was that participants with milder Parkinson's appeared to benefit.

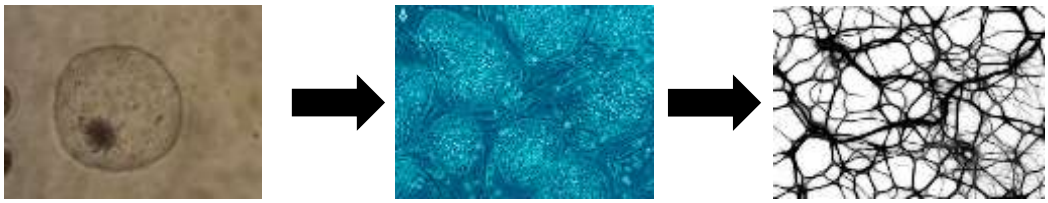
Based on these studies, it was concluded that fetal dopaminergic neurons **did not provide significant benefits** to people with Parkinson's, although there may be benefits in people with milder forms of Parkinson's. This is the general view on fetal dopaminergic neuron transplants today.

The main advantage to using fetal dopaminergic neurons is that since people with milder Parkinson's may benefit, further research into different methods might improve the results for all. Yet several daunting problems remain, including (1) the **ethical issue** of obtaining fetal dopaminergic neurons from aborted fetuses, (2) there are **not enough fetuses** to provide enough fetal dopaminergic neurons for large numbers of people to be treated, and (3) the **graft-induced dyskinesias**.

The chapter is not closed on fetal dopaminergic neurons - in 2015, another human study called TRANSNEURO commenced in Europe. Some enthusiasm persists.

Embryonic Donor Sources - Embryonic Stem Cells

Since 2000, it has been possible to isolate **embryonic stem cells** from pre-implantation human embryos. It is hoped that these cells could be transplanted into a human brain, where they would differentiate into dopaminergic neurons and release dopamine.



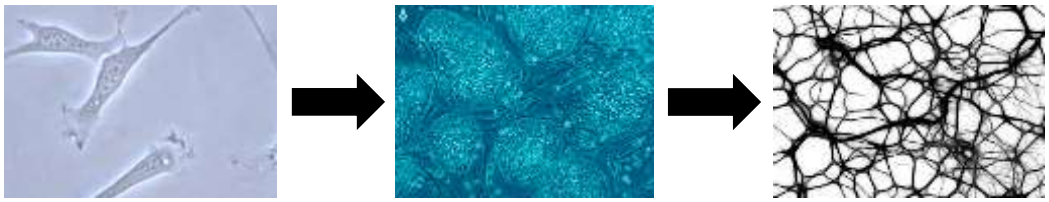
Human embryo | Embryonic stem cell | Dopaminergic neuron

Several studies have shown that human embryonic stem cells can **modestly improve motor defects** in "Parkinson's rats" and non-human primates. There are no human studies yet.

The main advantage to embryonic stem cells is that they may be less ethically contentious and able to provide larger quantities of cells compared to fetal dopaminergic neurons. Yet several major problems still plague embryonic stem cells, including (1) there remains an **ethical issue** of obtaining them from human embryos, (2) they may form **tumours**, and (3) they are susceptible to **immune rejection**.

Adult Donor Sources - Induced Pluripotent Stem Cells

In 2006, it was discovered that connective tissue cells could be "reprogrammed" to form **induced pluripotent stem cells**. In theory, connective tissue cells (or any other cell) could be taken from a person with Parkinson's, reprogrammed into pluripotent stem cells, and transplanted back into the brain in the hopes that they would differentiate into dopaminergic neurons and release dopamine.



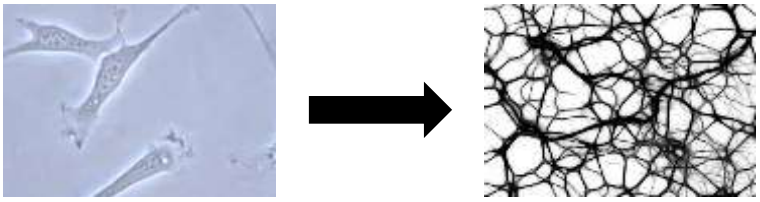
Adult connective tissue cell Pluripotent stem cell Dopaminergic neuron

While several studies have shown that induced pluripotent stem cells can **improve motor defects** in "Parkinson's rats" and non-human primates, there are no human studies yet.

The main clear advantage to using induced pluripotent stem cells is that the contentious ethical issues are circumvented, since the cells are harvested from the person with Parkinson's. However, there are still problems with induced pluripotent stem cells, namely that (1) the reprogramming process is **complicated**, (2) they may form **tumours**, and (3) they may harbour **gene mutations**.

Adult Donor Sources - Directly Induced Dopaminergic Neurons

In 2011, it was shown that mouse and human connective tissue cells could be reprogrammed directly, without being converted into pluripotent stem cells first, to form **directly induced dopaminergic neurons**. In theory, connective tissue cells (or any other cell) could be taken from a person with Parkinson's and directly reprogrammed to create dopaminergic neurons, which would then be transplanted back into the brain in the hopes that they would continue to release dopamine.



Adult connective tissue cell Dopaminergic neuron

Although the creation of directly induced dopaminergic neurons is a reality, there are no studies in animals or humans yet.

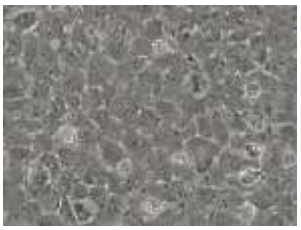
The advantage to directly induced dopaminergic neurons is that not only would they circumvent the ethical issues that plague most cell transplant therapies, the reprogramming process would also be less complicated and they might avoid the problem of tumour formation. The main foreseeable problem with directly induced dopaminergic neurons is that they may harbour **gene mutations.**

Adult Donor Sources - Past Failures, Future Possibilities

Fetal dopaminergic cells, embryonic stem cells, induced pluripotent stem cells, and directly induced dopaminergic neurons are not the only cell transplant therapies that have been studied.

A variety of other therapies using cells sourced from human adults have been tried in people with Parkinson's, including **carotid body cells** (from the carotid artery of the patient), **retinal pigment epithelial cells** (from the retina of the patient), and **adrenal medulla cells** (from the adrenal gland of the patient). They have all failed.

Two potential therapies using cells sourced from human adults remain. The first involves using adult **bone marrow stem cells**, which have yet to be shown to be able to make dopaminergic neurons. The second involves using adult **brain stem cells** from the hippocampus and subventricular zone, two human brain regions that appear to undergo continual neurogenesis throughout a person's life. Both therapies have potential, but that is all they have for now.



Replacing damaged neurons with bone marrow stem cells (left) or brain stem cells (right)?

Let us wrap up by making a few bold conclusions regarding cell transplant therapies. Although much research has been done on fetal and embryonic donor sources, the ethical issues surrounding **fetal dopaminergic neurons** and **embryonic stem cells** are simply too contentious to ever allow them to be reliable tissue sources. Moreover, while the concept of **induced pluripotent stem cells** is exciting since it circumvents the ethical issues, it is scientifically arrogant to believe that researchers will be able to fully control the fates of stem cells - to control life - in the near future, if ever. Thus, the concept of **directly induced dopaminergic neurons** may be the most appealing out of all the cell transplant therapies, if clinically effective transplants are ever shown to be feasible in people with Parkinson's.

At the risk of dampening the enthusiasm for cell transplant therapies even more, let us not forget that even if these considerable issues are overcome, two main problems with cell transplant therapies for Parkinson's remain - it is **a disease of neurons**, including neurons throughout the autonomic and enteric nervous systems, and it **damages non-dopaminergic neurons**, including the ones that store a person's unique memories. Cell transplant therapies cannot bypass these two problems.

So, my friends, **let us not wait in hope** for a miracle cure that is not likely to arrive in our lifetime. There are many other things that a person with Parkinson's can do now, **themselves**, by combining knowledge with action, rather than waiting in hope while researchers continue to experiment. There is no power in hope alone; it must be combined with action.

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References

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