



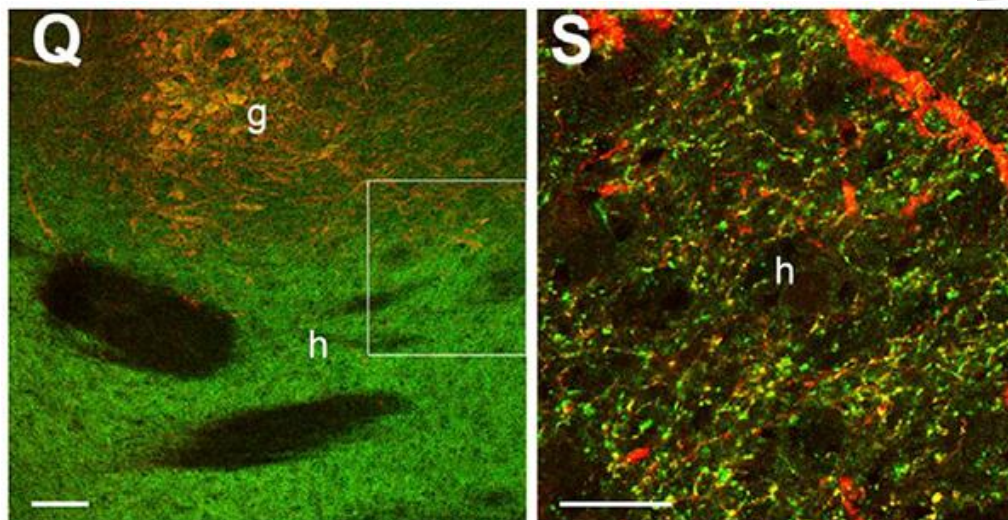
Fetal Dopamine Grafts for Parkinson's Remain Healthy After a Decade

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After falling out of favor for a decade, cell replacement therapy for Parkinson's disease appears poised to stage a comeback. The reason? Evidence of long-term survival of grafted fetal dopaminergic neurons. In the June 26 Cell Reports, researchers led by Ole Isacson of Harvard Medical School's McLean Hospital, Belmont, Massachusetts, add more data that grafts remain functional in patients more than 10 years after transplantation. In postmortem brains, the authors found robust innervation of the striatum by the transplanted neurons. Moreover, these neurons had maintained their normal shape and size, as well as a normal distribution of mitochondria, in stark contrast to the degeneration of nearby native dopamine neurons.

The data support plans by several groups to renew cell-replacement studies for Parkinson's, this time using dopamine neurons derived from stem cells instead of fetal neurons, Isacson told Alzforum. "Transplanting young, post-mitotic neurons into the circuitry of Parkinson's patients is reasonable and effective, and the cells can withstand whatever disease process is ongoing," he said.

At least some researchers agree. "The message from fetal cell transplants is that the transplanted neurons last for the rest of the patient's life. This paper is very encouraging for the long-term value of dopamine cell transplantation," said Curt Freed at the University of Colorado Health Science Center, Denver, a pioneer in the transplant field.



Dopamine neurons (red) in the graft (g) extend axons to innervate host striatum (h). Axon terminals express dopamine transporter (green) 14 years after transplantation. Low magnification (left panel) and high magnification (right panel).

More than 300 patients received fetal dopamine grafts in the 1990s and early 2000s. Many responded well and were able to reduce or stop medication. However, some patients did not improve, and about half of the recipients eventually developed dyskinesias, or involuntary movements. Postmortem studies fueled fears that the grafts were succumbing to Parkinson's disease, as a small fraction of transplanted neurons developed Lewy bodies, the characteristic

α -synuclein deposits of PD (see [Apr 2008 news story](#); [Apr 2011 conference story](#)). In one patient with a 22-year-old graft that had never provided a clinical benefit, almost half of the grafted neurons failed to express the dopamine transporter and appeared to be degenerating (see [Kurowska et al., 2011](#)).

Other studies belied these reports. In 2008, Isacson's group reported finding no evidence of Lewy bodies in grafts (see [Mendez et al., 2008](#)). A PET imaging study revealed that grafts restored brain dopamine levels for up to 16 years (see [Apr 2012 news story](#)). In addition, some grafts continue to help patients move better more than 20 years after transplantation (see [Jan 2014 news story](#)).

To revisit the question of the transplant's health, Isacson and colleagues took a more detailed look at grafts in the postmortem brains of four patients, which had been reported to be free of α -synuclein deposits in the 2008 paper. For two patients, the grafts were four years old at the time of death; these patients died of causes unrelated to PD. The grafts were nine and 14 years old, respectively, in the other two patients; they died of PD.

First author Penelope Hallett stained for dopamine transporters (DATs) in the axon terminals of transplanted neurons. Expression remained high in all four grafts (see image). DAT at the synapse takes up released dopamine and is crucial for regulating signaling and neurotransmission. Its presence at nerve terminals in the re-innervated striatum suggests the neurons remained functional, the authors claim. Typically, nerve terminals degenerate early in PD, before neurons die.

The authors then stained for mitochondrial markers. In surviving native dopamine neurons, mitochondria appeared only around the nucleus, while in transplanted neurons, mitochondria spread throughout the cell body, axon, and dendrites. Since mitochondria provide energy to the cell, their distribution is an indicator of the cell's health, the authors note. Moreover, transplanted neurons had normal shapes, sizes, and processes, in contrast to native neurons, which looked shrunken.

These data from four human brains seem to counter data from animal studies showing that aggregated α -synuclein can spread through brains and corrupt native protein (see [Apr 2012 news story](#); [Nov 2012 news story](#); [Mar 2013 conference story](#)). While transmission of aggregated α -synuclein may occur in human brains too, it seems not to have much effect on neuron function over the course of 10 or 20 years, Freed noted. His group has by now examined transplants in 14 postmortem brains, the largest set from any research group. "We see occasional Lewy bodies, and yet find that the dopamine neurons are healthy and are resupplying brain," he said.

These findings have renewed interest in performing transplants using dopamine neurons derived from either embryonic or induced pluripotent stem cells (see [Jul 2011 news story](#); [Nov 2011 news story](#)). Stem cells will provide a more reliable source of cells than fetal tissue, and potentially could be scaled up to treat thousands of patients, Freed said. Several groups around the world are working on this. In an email to Alzforum, Thomas Foltynie at University College London wrote, "The [TRANSEURO](#) team are about to embark on a further series of fetal dopamine cell transplants in younger PD patients at an earlier stage of disease." (See full comment below.) Meanwhile, Isacson is performing stem cell-derived neuron transplants in monkeys to find the right dose and protocol. At a recent conference hosted by the California Institute for Regenerative Medicine, experts agreed that human transplants might resume in 2016 or 2017, Freed said. α -synuclein

COMMENTS

Comments on this content

[Thomas Foltynie](#) UCL Institute of Neurology

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These data add to our confidence that cell therapy might re-emerge as a potentially useful therapy in PD following the disappointments of two double-blind trials. In this latest paper, Dr. Isacson has shown that transplanted fetal dopaminergic cells remain healthy and functional many years after the transplant procedure. The publication is timely as the TRANSEURO team are about to embark on a further series of fetal dopamine cell transplants in younger PD patients at an earlier stage of disease. It is hoped that positive results will pave the way for trials of stem cell transplants to replace fetal cells as a more acceptable way of repairing the dopaminergic deficits seen in PD.
