

# Novel therapies in the search for a cure for Huntington's disease

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The present era is one of tremendous excitement and rapid innovation in Huntington's disease (HD) research. The pace of research seems to be rapidly quickening. The discovery of the gene and the subsequent development of transgenic mouse models of HD have been major breakthroughs. Now, after a large number of experimental studies in animals, a few pilot clinical trials have been initiated. The work presented by Freeman *et al.* (1) in a recent issue of PNAS reports the survival and development of a graft, derived from human fetal striatal, in a patient with HD.

The molecular basis of HD, and at least seven other diseases, that renders it amenable to potential gene therapy techniques involves the expansion of a CAG repeat in the genome, leading to the production of a mutant protein with an expanded polyglutamine repeat. It is now evident that changes in gene expression occur early in polyglutamine diseases, as early as 1 day after the initial expression of the mutant gene in animal models (2). Recent studies have demonstrated that huntingtin, as well as other polyglutamine-containing proteins, can directly interact with transcription factors. Of particular interest, the HD protein has been shown to directly interact with P53 and CREB-binding protein (CBP) (3). This interaction then represses transcription. In studies of cell culture and transgenic mouse models of spinal and bulbar muscular atrophy, it has been demonstrated that the CBP is incorporated into nuclear inclusions formed by polyglutamine-containing proteins and cultured cells (4). It is also found in intranuclear inclusions in tissue from patients with spinal and bulbar muscular atrophy. The CBP is also incorporated into nuclear inclusions found in a cell culture model of spinocerebellar ataxia type 3. Overexpression of CBP rescues cells from polyglutamine toxicity. CBP is an important transcriptional coactivator that orchestrates nuclear responses to a variety of cell signaling cascades, and it has been identified as a critical component of neuronal responses to neurotrophins. It is, therefore,

possible that CBP is sequestered in polyglutamine diseases, resulting in a diminished response to trophic factors, which are essential for neuronal survival.

Despite this rapidly expanding knowledge about the cellular effects of polyglutamine-expanded proteins, therapy for HD remains elusive. The study of therapeutics in the transgenic mouse models however, has led to a number of interesting leads. It has been shown that inhibitors of caspases and crossing the R6/2 transgenic mouse model of HD with a dominant/negative inhibitor of caspase 1 significantly improve survival of these mice (5). It has also been demonstrated that administration of minocycline, which reduces the transcription of both caspases and the inducible form of nitric oxide synthase, exerts significant neuroprotective effects in the R6/2 mice (6). Because energy dysregulation may play a role in HD pathogenesis, we examined whether creatine, which can buffer cellular energy levels, can exert neuroprotective effects in the R6/2 and the N171-82Q transgenic mouse models of HD (7). We found marked significant neuroprotective effects in both of these transgenic mouse models of HD. We found that creatine delays weight loss, improves motor performance, delays the onset of diabetes, reduces the formation of intranuclear inclusions, delays striatal atrophy, and significantly improves survival. The prospects for neuroprotective treatment in HD patients are, therefore, rapidly brightening. Nevertheless, at present there is no proven effective therapy. A promising approach to HD therapeutics is neural transplantation.

The possible clinical application of neural grafting in neurodegenerative diseases was first suggested a little more than 20 years ago when it was reported that striatal implants of

dopamine-rich ventral mesencephalic tissue from rat fetuses could reduce symptoms in a rat model of Parkinson's disease (PD) (8, 9). Since then, it has been convincingly demonstrated that fetal nigral grafts can survive, secrete dopamine, form synaptic connections with host neurons, and reverse

behavioral deficits in experimental models of PD in small laboratory animals as well as in large non-human primates in pre-clinical trials. This large body of encouraging experimental data prompted several teams to initiate clinical trials in PD patients in the 90s

(10–12). However, whereas these initial trials revealed that PD patients may clearly benefit from neural transplantation, the observed benefits were inconsistent and in some cases modest. Apart from specific variables in the procedure, such as donor age and number of fetuses, preparation of the fetal tissue, and immunosuppression, that were not standardized, this variation in the clinical response could also be related to differences in the survival of implanted dopamine neurons, which has been shown to be critical for functional recovery in animal models (13, 14). In 1995, Jeff Kordower, Tom Freeman, and collaborators published neuropathological evidence of graft survival and striatal reinnervation after transplantation of fetal mesencephalic tissue in a patient with PD (15). This study reported that, after transplantation, in a patient who had sustained improvement in motor function and a progressive increase in 18F-fluorodopa uptake in the putamen on positron-emission tomography (PET) scanning, each of the grafts appeared viable on postmortem examination of the brain. Most impor-

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tantly, the grafts appeared well integrated within the host striatum, extending processes out of the grafts and providing extensive dopaminergic reinnervation to the host striatum. This report by Kordower *et al.* was critical in demonstrating that grafted dopamine neurons can survive and grow in the human brain and provide functional recovery. Ten years after the first reports of positive clinical results, it is now clear that consistent improvement in clinical features and dopamine function can be obtained following fetal tissue transplantation in patients with advanced PD (16–18).

HD has been for 15 years considered as another disease potentially amenable to cell therapy. The report by Freeman *et al.* describes the postmortem histological analysis of fetal striatal grafts implanted in the striatum (caudate-putamen) of one of these patients (1). HD is a genetic disorder, primarily characterized by neuronal degeneration in the striatum. The rationale of neural grafting in HD largely differs from the strategy used in the case of PD because grafted neurons have to substitute completely for degenerated cells in the former, whereas they are expected to provide reinnervation only of the host area in the latter case. Therefore, the use of intrastriatal grafting for the treatment of HD is largely based on the observation that at least a partial reconstruction of the cortico-striato-pallidal

neural circuit is necessary for functional recovery to occur. In rodents (19–21) as well as in non-human primates (22–24), striatal xenografts and allografts implanted into the lesioned striatum have been shown to survive, integrate into the host brain circuitry, and improve motor and cognitive functions. Like normal striatal neurons, grafted cells receive topographically organized cortical inputs and establish efferent projections to appropriate striatal targets (in particular the globus pallidus and the substantia nigra pars reticulata). Several studies have demonstrated that the reconstruction of neural circuitry can be physiologically active and can at least partly normalize the metabolic hyperactivity in the extrapyramidal neuronal system induced by the striatal degeneration (25). In line with this need to reconstruct neural circuitry, Freeman and collaborators (1) are to be congratulated for their demonstration that human striatal cells can survive and develop appropriately in the striatum of a patient with HD.

They had the unique opportunity to examine postmortem a HD patient who had received fetal striatal transplants 18 months before death. The findings are significant in several respects. The authors demonstrated that immature fetal striatal tissue can survive and differentiate into full and mature striatal tissue in HD brain.

They also demonstrated that several types of neuronal phenotypes that are characteristic of the normal striatum are present in the striatal grafts. Furthermore, they found that transplant regions were clearly innervated by host tyrosine hydroxylase fibers, suggesting that they could reestablish afferent connections. Another important observation was that the striatal allografts survived long-term for 18 mo without any signs of immune rejection, despite the fact that immunosuppressive treatment was maintained only within the first 6 months. Lastly, the authors made the observations that the grafted neurons did not develop any neuronal intranuclear inclusions and that there were no signs of any neuronal degeneration in the graft.

As pointed out by the authors, this result conceptually supports the use of striatal tissue implantation as a novel therapy for patients with HD. These neuropathological results are timely because a French team, working in parallel, found in a pilot study that striatal grafts produce long-lasting motor, cognitive, and functional benefits in grafted HD patients (26). These findings, therefore, suggest that striatal transplantation may be viable treatment for HD patients. The rapid advances in understanding the pathogenesis of HD, experimental therapeutics, and now neural transplantation augur a bright future for finding a cure for this devastating illness.

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