



NEURODEGENERATIVE DISORDERS: GENE THERAPY ON CLINICAL TRIAL

By Patrick Aebischer

Our molecular understanding of neurodegenerative diseases has made remarkable progress during the last decade. The genetic cause of diseases such as Huntington's or spinal muscular atrophy has been unraveled. Numerous gene defects have been identified for the familial forms of amyotrophic lateral sclerosis, fronto-temporal dementia, Alzheimer's and Parkinson's disease. In parallel, lentiviral viral vectors and adeno-associated vectors have been developed to the point that they can be safely considered for *in vivo* gene therapy clinical trials. Based on encouraging results obtained in primate models of Parkinson's disease (Jarraya et al., 2009), two clinical trials have been recently performed. The first one used equine infec-

tious anemia virus (EIAV), a lentivirus, as a transfer vector for the striatal expression of key enzymes involved in the production of dopamine. The second one is based on the use of adeno-associated vectors type 2 for the striatal expression of neurturin, a dopaminergic trophic factor (Marks et al., 2008). Whereas these two approaches aim primarily at ameliorating the symptoms, no trial has attempted to correct the cause of the disease. Parkinson's disease constitutes an ideal case for gene therapy as its target, the substantia nigra pars compacta, is well defined and contains a small number of cells to be infected (less than one million dopaminergic nigral neurons). It remains to be elucidated which gene should be inves-

tigated for preventing neuronal demise. The first genes that come to mind are those involved in recessive forms of familial Parkinson's disease, namely parkin and

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pink1, whose overexpression may compensate for a loss of function. The small number of patients and the slow evolution of the disease question this approach. Whereas the down-regulation of α -synuclein (α -Syn) using RNAi technology seems a promising approach, the recent observation in rodents that α -Syn silencing leads to a loss of nigral dopaminergic neurons in rodents has raised concerns about this strategy (Gorbatyuk et al., 2009). Other neurodegenerative diseases, such as Huntington's or Alzheimer's disease, will require infection of a large number of spread neurons – a presently unresolved technical problem.

The most promising diseases may paradoxically be those affecting motoneurons. Whereas Foust et al. (2009) have reported that the intravascular AAV-9 preferentially targets neonatal and adult astrocytes, Chris Towne in our laboratory has recently

observed that the intrathecal injection of AAV-6 results in a very large number of motoneurons infected all along the spinal cord of rodents (Figure 1). Promising results have been observed in mouse models of spinal muscular atrophy by the overexpression of the *smn* gene. However, scale-up of the system to primates is required before moving to the clinic. Familial amyotrophic lateral sclerosis caused by mutations in the copper zinc superoxide dismutase could also benefit from this approach.

While basic science will provide us with more genes to test, we need to continue our quest to further improve our viral vectors so that they can accommodate larger genes, diffuse over longer distances and infect a specific subpopulation of nerve cells. The rationale to use gene therapy for treating the cause of neurodegenerative is sound. We just need more sweat and hard work. 🧑🏻‍🔬

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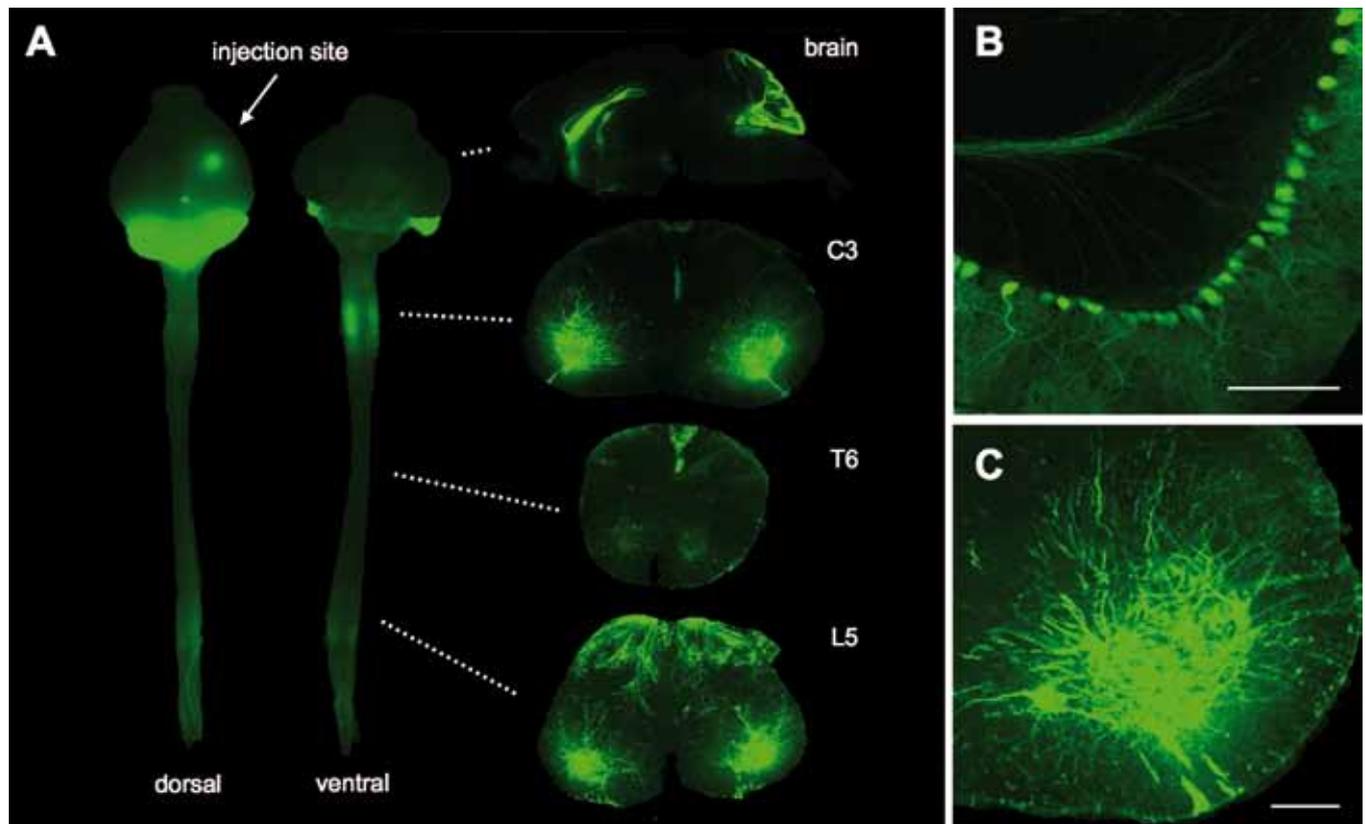


Figure 1. (A) ICV injection of AAV6-GFP results in widespread GFP expression across the brain and spinal cord. High magnification indicating transduction of (B) Purkinje cells of the cerebellum and (C) motor neurons of the spinal cord ventral horn. Scale bar = 100 μm.