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Going 'nano' on Parkinson's disease in Mexico

The Center for Research and Advanced Studies (Cinvestav) is a national leader in scientific research, technology development and the formation of highly educated professionals in Mexico. Cinvestav is now expanding its reach globally with a nanoparticle-based therapy for Parkinson's disease that represents an opportunity for international partnerships.

Cinvestav focuses on the natural and biological sciences, health, engineering and social sciences, completing these areas with a number of multidisciplinary programs. Cinvestav has ten campuses across the country, each focusing on a particular research subject according to regional needs and industrial development. Its areas of influence range from metallurgy and information technologies to biodiversity and marine resources.

Cinvestav fosters and supports the transfer of knowledge from its scientists and laboratories to the industrial sector through its knowledge transfer and commercialization office, the 3C agency, which aims to provide a framework both for scientists to collaborate with industry and for scientists to spin out their own companies.

3C's portfolio includes technologies such as smart nanoparticles for gene therapy; blood-based diagnosis for trichomoniasis; early-stage diagnosis of cervical cancer; novel therapeutics for metabolic syndrome; a synthetic derivative of amphotericin B; and a platform for the expression, production and scaling up of recombinant proteins.

"Cinvestav has been an engine for the development of the high-tech industry in Mexico, particularly in the areas of electronics, telecommunications, plant biotechnology, aquaculture and artificial skin; many of these developments have now been transferred to companies located in the US," said Jose Luis Leyva, secretary of strategic planning at Cinvestav. "Cinvestav continually offers its scientific findings to industry to convert them into products that would benefit society. Cinvestav's objective is to become a research center considered as a reference in the world for knowledge transfer and innovation."

Nano-attack on Parkinson's disease

Nanoparticle-based drug delivery systems have attracted great interest over the past decade as a way to improve therapeutic indexes by increasing the specificity with which a drug is delivered to target cells. Nanoparticles can be used to deliver a range of therapeutic compounds, including small molecules and nucleic acids (genes). One of the biggest challenges has been to design nanoparticles capable of targeting therapeutic genes to dopaminergic neurons of the brain.

Researchers at Cinvestav led by Daniel Martinez-Fong have now developed a synthetic nanoparticle that can deliver genes directly and specifically to dopaminergic neurons of the substantia nigra in the brain. The nanoparticle is a neurotensin polyplex consisting of compacted plasmid DNA encoding the gene for brain-derived neurotrophic factor (BDNF) surrounded by three peptides. The peptides target dopaminergic neurons via neurotensin receptor type 1 and deliver the plasmid payload to the cell nucleus after internalization of the receptor (**Fig. 1**). The nanoparticle, dubbed Cinvestav-PX-001, is being applied to the treatment of Parkinson's disease (PD).

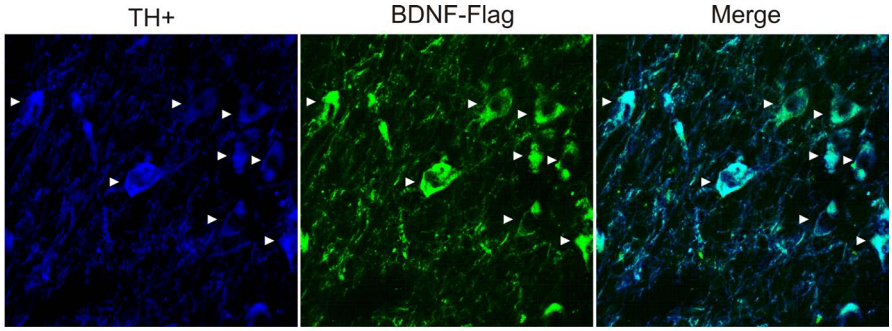

Figure 1: Cinvestav-PX-001 is a nanoparticle-based vector for the treatment of PD. Tyrosine-hydroxylase-positive (TH+) dopaminergic neurons in the substantia nigra (blue-stained cells; left panel) are targeted by Cinvestav-PX-001 (green-stained cells; middle panel), enabling highly specific BDNF replacement therapy in damaged neurons in subjects with PD (right panel). Modified from ref. 2.

PD is a progressive neurodegenerative disease associated with severe motor and cognitive symptoms caused by the death of dopaminergic neurons in the substantia nigra. Current therapeutic options such as dopamine-replacement drugs provide only symptomatic improvement, without affecting progressive neuronal loss, and are characterized by decreased efficacy and the emergence of serious adverse side effects with continued administration.

Reduced expression of BDNF is known to contribute to the death of dopaminergic neurons in PD, and thus replacement therapy with BDNF has been proposed as a potential way to prevent the progression of PD.

Overexpression of the gene that encodes BDNF has been shown to slow down[1] and even reverse[2] PD in preclinical disease models using a single dose of Cinvestav-PX-001 as a gene delivery system. Remarkably, the profound neuroregenerative effect leads to complete recovery of normal motion[1], even in animals with advanced-stage disease[2].

Cinvestav-PX-001 now provides an alternative to viral vectors that offers great promise as a treatment for PD because of its strong neuroregenerative effect on dopamine neurons of the substantia nigra.

Going into the clinic

Cinvestav-PX-001 has shown great specificity in neuronal delivery, is cost-effective to synthesize and has an optimal biosafety profile, all of which make it an excellent alternative to viral vectors for PD treatment.

Cinvestav is now looking for a partner to perform the necessary phase 1 and phase 2 trials in humans. The ideal partner would have the capabilities and experience to run such trials internationally. Cinvestav is planning to spin out a locally funded company around the nanoparticle technology and is in a position to offer a non-exclusive license to conduct the trials.

"We are looking for a win-win partnership that allows us to put a new therapy on the market that could help the people living with Parkinson's disease and provide them with a better quality of life," said Leyva. "At the same time, we would also like to establish a new and productive business that not only benefits the stakeholders but also generates resources to finance new scientific research to treat other diseases."

1. Hernández-Chan, N.G. *et al. J. Biomed. Sci.* **22**, 59–72 (2015).
2. Razgado-Hernández, L.F. *et al. PLoS ONE* **10**, e0117391 (2015).

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