



U.S. Department of Veterans Affairs

Veterans Health Administration  
Parkinson's Disease Research,  
Education & Clinical Centers

NATIONAL VA PARKINSON'S DISEASE

C O N S O R T I U M

Education · Collaboration · Advocacy

# THE TRANSMITTER

*November 2022*

## Article Reviews

*Prepared by: Adrienne Keener, MD; Katherine Fu, MD (Senior PADRECC Fellow); & Danielle Thordarson, MD (Junior PADRECC Fellow) ~ Southwest PADRECC*

### **Putaminal Recombinant Glucocerebrosidase Delivery with Magnetic Resonance–Guided Focused Ultrasound in Parkinson's Disease: A Phase I Study**

*GBA1* mutation is the most common genetic risk factor for Parkinson's disease (PD), as up to 10% of patients with PD may have a *GBA1* mutation. Glucocerebrosidase (GCase) deficit has been demonstrated in brains of PD patients with *GBA1* mutations as well as those with idiopathic PD, and so GCase replacement may serve as a potential approach to a disease modifying therapy in PD. Unfortunately, the intravenous recombinant GCase used in Gaucher Disease has poor blood brain barrier (BBB) penetration, thus leading to this study, which aimed to explore the safety and feasibility of unilateral putaminal delivery of GCase with magnetic resonance guided focused ultrasound (MRgFUS) in patients with PD and *GBA1* mutations. This was an open-label, phase I, single-arm intervention trial investigating the MRgFUS putaminal delivery of intravenous GCase (Cerezyme® [imiglucerase]) at escalating doses (15 to 30 to 60 IU/kg) every 2 weeks in four patients. The BBB was reconstituted in all patients within 24 hours by qualitative analysis and within 1 week by dynamic-contrast enhanced (DCE) MRI analysis, demonstrating that MRgFUS did not affect long-term BBB integrity in PD. No SAE was detected, and only transient worsening or new dyskinesia was observed in two patients, possibly related to an increase in levodopa or an increase in levodopa exposure as a result of the BBB opening. Overall, this study supported the safety and feasibility of MRgFUS GCase delivery in PD, though future larger studies will be needed to better characterize the safety, clinical, and imaging effects of this approach.

*Meng, Y., Pople, C. B., Huang, Y., Jones, R. M., Ottoy, J., Goubran, M., ... & Kalia, L. V. (2022). Putaminal Recombinant Glucocerebrosidase Delivery with Magnetic Resonance–Guided Focused Ultrasound in Parkinson's Disease: A Phase I Study. Movement Disorders.*

<https://pubmed.ncbi.nlm.nih.gov/36089809/>

## **TRAX Provides Neuroprotection for Huntington's Disease Via Modulating a Novel Subset of MicroRNAs**

The accumulation of mutant HTT protein aggregates in Huntington's disease impairs microRNA biogenesis, leading to neuronal dysfunction. Overexpression of several microRNAs may be protective in the initial stages of HD, lowering the levels of mHTT and reducing the toxicity mediated by mHTT inclusions. Translin-associated protein X (TRAX) is a scaffold protein that performs a variety of intracellular functions, including suppressing microRNA-mediated silencing and regulating RNA trafficking in neurons.

In the present study, the authors sought to clarify the role of TRAX in Huntington's disease pathogenesis. First, TRAX expression in the brains of humans and mouse models of HD was detected by immunohistochemistry staining, demonstrating significantly elevated levels of TRAX in the caudate and putamen of post-mortem HD patients and HD mouse models as compared to their unaffected counterparts. Next, TRAX expression was downregulated by delivering TRAX short hairpin RNA via a viral vector in HD mice at 5 weeks of age. Behavioral parameters of motor function were monitored in all mice, and at 12 weeks of age, the striatum was collected for microRNA and mRNA sequencing. TRAX downregulated mice had enhanced expression of 83 microRNAs and in turn differential expression of mRNAs involved in HD pathogenesis, including DARPP-32 and brain derived neurotrophic factor. In addition, TRAX-downregulated HD mice had accelerated motor decline with worsened rotarod performance and clasping as compared to HD mice with normal TRAX function. Suppression of TRAX also markedly increased the accumulation of mutant HTT protein in the striatum. Taken together, these results support that TRAX plays a protective role in HD by regulating microRNA biogenesis. Further investigation is needed to delineate how TRAX is regulated in normal aging and neurodegeneration with the hope of harnessing this protective protein to develop novel therapeutics in neurodegenerative diseases such as Huntington's disease.

*Weng YT, Chen HM, Chien T, Chiu FL, Kuo HC, Chern Y. TRAX Provides Neuroprotection for Huntington's Disease Via Modulating a Novel Subset of MicroRNAs. Mov Disord. 2022 Oct; 37(10):2008-2020. doi: 10.1002/mds.29174. PMID: 35997316.*

## **Validation of the OPTIMIPARK Questionnaire: A Tool to Optimize Treatment in Parkinson's Disease**

In this study, the authors aim to validate a self-administered questionnaire, OPTIMIPARK, to assess dopamine-responsive motor and non-motor symptoms in Parkinson's disease (PD) and inform clinical decision making. This was an observational, cross-sectional, multicenter study, which enrolled 113 patients with PD (62.8% men, mean age 66 years). The OPTIMIPARK questionnaire consists of 9 items, rated by the patient according to severity – none (0), mild to moderate (1) or severe (2) with a goal of assessing the impact of motor fluctuations, as well as non-motor fluctuations including anxiety, pain, and fatigue. Disease-specific scales, including the MDS-UPDRS Parts I, II, and IV as well as the CISI-PD (Clinical Impression of Severity Index for PD) and the WOQ-19 (Wearing-off Questionnaire) were highly correlated with the OPTIMIPARK total scores; however, the association with the MDS-UPDRS Part II and HY scale was weak. In the study, one neurologist provided routine clinical care, considered the gold standard, and determined a therapeutic decision classified in one of the following

three categories: (1) “no changes”; (2) “adjustment of conventional treatment”, when medications were modified including addition of a new oral medication; or (3) “advanced therapy indicated”, when a patient was referred for continuous infusion or surgical treatment options. Separately, 2 external neurologists relied on basic demographic data (age, disease duration, and current treatment) along with the completed OPTIMIPARK questionnaires to recommend a therapeutic decision in one of the three categories above. Concordance between the clinical neurologist vs the OPTIMIPARK-based decisions of each external neurologist, as well as the consensus and interrater reliability between the two external neurologists were analyzed. OPTIMIPARK-based decisions showed a moderate agreement with the clinical decision (Kendall’s  $W = 0.77$ ), and OPTIMIPARK interrater reliability was high (87.6%;  $\kappa$ , 0.87). The main disagreements between the clinical decision and the OPTIMIPARK-based decision were in the “no changes” category, recommended 40% of the time by the clinical neurologist vs only 26% of the time by the external neurologists. The authors therefore conclude that the OPTIMIPARK questionnaire may be more sensitive in identifying patients who may require a change in treatment compared to standard clinical care. Future research is needed to determine appropriate cutoff scores for the OPTIMIPARK questionnaire, though the current results suggest that a score of 3 or 4 up to 6 may indicate a need to adjust conventional treatment, and a score of  $>6$  may indicate the need for advanced therapies. One advantage of this questionnaire is the ease of use (estimated to take only 5 minutes for patients to complete). The authors do note important limitations, however, particularly the need to take into account other PD motor and non-motor symptoms such as cognitive, mood, and balance issues, as well as patient preferences and caregiver burden when making a therapeutic decision. That said, the OPTIMIPARK questionnaire may be a helpful complimentary tool to supplement clinical judgement.

*Máñez-Miró, J.U., Vivancos-Matellano, F., Alonso-Frech, F., Vela-Desojo, L., López-Ariztegui, N., López-Manzanares, L., Balaguer, E., Martínez-Castrillo, J.C., Herrero-Infante, Y., Gasca-Salas, C., Morales-Casado, M.I., Casas, E., Hernández, A., Pareés, I., Tegel-Ayuela, I., Martínez-Fernández, R. and Martinez-Martin, P. (2022), Validation of the OPTIMIPARK Questionnaire: A Tool to Optimize Treatment in Parkinson's Disease. Mov Disord Clin Pract, 9: 1085-1093. <https://doi.org/10.1002/mdc3.13581>*

## **Committee Activities**

### **Clinical Care Committee**

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The Northwest PADRECC leads the committee for November/December. The committee meets via conference call the first Tuesday of the month at 12pm (EST)
- **Standardize and Optimize Clinical Care:** The committee continues to discuss treatment strategies, new medications and other procedures, and other clinical issues to improve patient care and outcomes across the national PADRECCs service area. It also serves to provide clinical support to the consortium network by focusing on procedures and measures to standardize clinical care across the PADRECC network.

- Recent agenda items have included:
  1. Future planning to enhance clinical service provision at PADRECCs : Suggestions and Strategies
  2. Discussion of DBS management and surgical programs at the PADRECCs

## Education Committee

- **PADRECC/EES Movement Disorder Series-Webinars:** knowledge-based webinars to provide VHA healthcare professionals with current practice standards and emerging trends in the treatment of Parkinson's disease and other movement disorders. CEs are typically provided for the live webinars. Check out the following link for a list of past webinars and if you are interested in receiving a recording of a past webinar please email [Gretchen.glenn@va.gov](mailto:Gretchen.glenn@va.gov) and list the date/topic of interest: [https://www.parkinsons.va.gov/Consortium/Presentations/Audio\\_Conference/MDS.asp](https://www.parkinsons.va.gov/Consortium/Presentations/Audio_Conference/MDS.asp)
  - **Update-Movement Disorders Series Part II Webinar** was held on October 13th, 2022 and had an astounding 517 participants registered!
  - **SAVE THE DATE - Movement Disorders Series Part III-Webinar- Non-Motor Symptoms of PD** - February 9<sup>th</sup>, 2023- 9am-1pm PST / 12pm-4pm EST
  - **Registration Now Open - Philadelphia VA PADRECC/MIRECC Symposium/Webinar: Lifestyle Interventions to Promote Brain Health in Neuropsychiatric Disorders-** March 22, 2023 - 8am - 12pm PST / 11am - 3pm EST
- **Caregiving 101: An Introduction to Your Caregiving Journey-** This webinar was held on November 2<sup>nd</sup>, 2022 and was offered nationally to all PD care partners.
- **VHA/PADRECC & The Parkinson's Foundation Partnership:** Goal of the partnership is to improve the care and quality of life for Veterans living with PD through collaborative education, research and services. This committee spearheads many of the projects for this partnership. Please check out the Transmitter email for current partnership offerings/activities
- **National Website Maintenance:** The committee performs periodic maintenance checks of the National Website to ensure information is current and up-to-date.
- **PADRECC Transmitter:** This committee continues to assemble and distribute this *e*-newsletter every other month.
- **Resources available on the National Website:**
  - **Patient Education Brochures-** <https://www.parkinsons.va.gov/patients.asp>
    - Exercise and Physical Activity
    - Fall Prevention
    - Motor Symptoms
    - Non-Motor Symptoms
    - Agent Orange and Toxic Exposures and PD

- **PADRECC Support/Education Groups:** The PADRECCs are now holding virtual groups open to Veterans and care partners interested in attending. Please check out the National Website for listing of dates/times and contact person to register for the groups and please share with your patients/care partners: <https://www.parkinsons.va.gov/patients.asp>
- **My Parkinson's Story-**<https://www.parkinsons.va.gov/patients.asp>  
A series of short videos prepared by the VA PADRECCs addressing various aspects of Parkinson's disease.
- **Suggested Education Essentials for Veterans with PD**
  - **Digital version:** <https://www.parkinsons.va.gov/patients.asp>



Suggested Education  
Essentials

- **Printer friendly version:**