Wang et al. *Zool. Res.* 2023, 44(6): 1152−1153
https://doi.org/10.24272/j.issn.2095-8137.2023.353

ZR | Zoological Research

Research highlight Open Access

Circuit-specific gene therapy is knocking on the door of Parkinson's disease

Parkinson's disease (PD) is a prevalent neurodegenerative disorder that affects millions of individuals worldwide. Symptoms of PD typically manifest as movement impairments, including bradykinesia, rigidity, tremors, and postural instability, as well as non-motor symptoms, such as cognitive decline, pain, and depression (Bloem et al., 2021). The fundamental neuropathological hallmarks of PD include the degeneration of dopaminergic neurons in the substantia nigra (SN) and the aggregation of α-synuclein in intracellular inclusions. At present, the primary interventions for PD treatment are levodopa, dopamine agonists, deep brain stimulation (DBS), and physical therapy. However, levodopa administration can lead to intractable side effects such as dyskinesia (Wang & Shih, 2023) and DBS poses risks of long-term psychiatric complications, including chronic depression and personality alterations, as well as infection related to the intracranial electrodes (Volkmann et al., 2010). Consequently, there exists an urgent need for the innovation of targeted and efficacious treatments for PD.

Chen et al. (2023) recently documented the development and verification of a novel gene therapy for PD, which successfully reversed the core motor symptoms of PD in both mouse and monkey models (Figure 1). Their research specifically targeted D1 medium spiny neurons (D1-MSNs) in the striatum, which project to the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr), thus forming a direct pathway. D2 medium spiny neurons (D2-MSNs), another important neuronal type in the striatum, project indirectly to the SNr via the globus pallidus external segment (GPe)/subthalamic nucleus (STN), thus forming an indirect pathway. Activation of the direct pathway (comparable to an "accelerator") facilitates movement, whereas activation of the indirect pathway (comparable to a "brake") inhibits movement. In PD, degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) weakens dopaminergic modulation of both D1-MSNs and D2-MSNs. As a result, the direct pathway is repressed while the indirect pathway is enhanced, causing an imbalance between the "accelerator" and "brake", resulting in motor deficits. Therefore, the study aimed to up-regulate the activity of D1-MSNs associated with the direct pathway and thereby restore movement control equilibrium in PD (Chen et al., 2023).

To achieve this objective, a method to precisely manipulate specific cell types within D1-MSNs is required. Thus, the authors utilized cell type-specific expression by employing a tailored retrograde adeno-associated virus (AAV) with a unique promoter to drive elevated gene expression in D1-MSNs, the only major cell type in the striatum projecting to the SNr. Specifically, the team first engineered several AAV capsid mutants, with the AAV8 mutant, AAV8R, showing improved retrograde infection of D1-MSNs. Subsequent modifications led to the identification of AAV8R12 as the most efficient mutant for labeling D1-MSNs. Next, the authors analyzed a gene expression database and screened for promoters. Through extensive *in vivo* experimentation, the authors ascertained that the *G88* promoter family drove the highest level of gene expression in MSNs. Consequently, by integrating the *G88P3*/*G88P7* promoter with the AAV8R12 vector, they obtained a robust manipulation tool capable of labeling D1-MSNs with strong specificity in primates.

Next, to modulate the functions of the labeled D1-MSNs, the authors expressed Designer Receptors Exclusively Activated by Designer Drugs (DREADD) effector rM3Ds into D1-MSNs by unilaterally injecting the viral vector AAV8R12-*G88P7*-*rM3Ds-2A-EYFP* into the SNr of monkeys. Following the administration of clozapine N-oxide (CNO) and deschloroclozapine (DCZ), ligands that bind with rM3Ds to enable neuronal excitation (Roth, 2016), the monkeys showed marked increases in contraversive rotations, thus demonstrating the efficiency of the toolkit in direct pathway activation.

Finally, the same approach was applied to MPP^+-treated monkeys, which exhibited PD-like symptoms, including tremor, bradykinesia, and rigidity. Following a single surgical procedure to inject the virus into the SNr, the monkeys receiving regular CNO/DCZ treatments showed rapid recovery and restored motor ability, including increased spontaneous movement, reduced tremor, and improved motor skills. Continuous monitoring of these subjects confirmed the long-term safety of the treatment. Notably, when compared to the standard therapeutic dose of levodopa, the most widely used treatment for PD, this circuit-specific gene therapy not only showed a more rapid reversal of symptoms but also no inducement of observable side effects.

Chen et al. (2023) not only established a proof-of-concept for circuit-specific therapeutics, but also effectively leveraged a non-human primate (NHP) model to fully showcase the

Received: 07 November 2023; Accepted: 15 November 2023; Online: 17 November 2023

Foundation items: This work was supported by the National Natural Science Foundation of China (32160204), Major Science and Technology Projects of Hainan Province (ZDKJ2021032), and STI 2030 —Major Projects (2022ZD0208602)

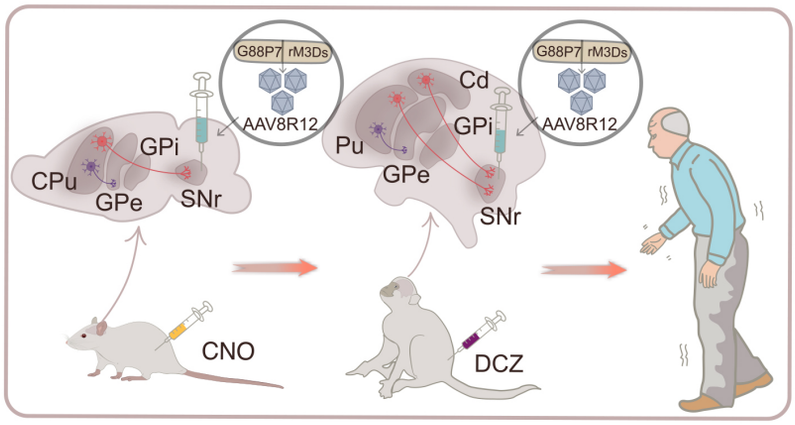

Figure 1 Circuit-specific gene therapy opens the door for a new era of Parkinson's disease (PD) therapeutics

effectiveness and safety of the therapy in PD monkeys. Given the natural occurrence of parkinsonian conditions in monkeys (Li et al., 2021a, 2021b), indicating shared mechanisms and pathologies of PD between NHPs and humans, this approach holds promise for successful clinical translation and application. In contrast, numerous proposed therapeutics have claimed efficacy in alleviating PD symptoms in mice. However, the significant physiological differences between mice and humans, coupled with the fact that mice do not naturally develop PD, have resulted in the failure of many of these mouse-based trials in the end. In this context, Chen et al. (2023) have laid a new foundation for translating cutting-edge biotechnology into feasible pre-clinical practice.

Furthermore, recent reports have highlighted various new therapeutic approaches for PD, with several advancing to stages of clinical trial validation. For example, Bayer recently announced positive Phase-I results for its stem cell-based therapy bemdaneprocel (BRT-DA01) for PD, encouraging progression to the next phase of clinical testing. Concurrently, several companies have been developing immunotherapies targeting α-synuclein. Among these, prasinezumab (PRX002), developed by Prothena and Roche, did not achieve the expected outcomes in its Phase-II trials. Nevertheless, PRX002 demonstrated potential signs of disease progression mitigation, such that the companies have resolved to continue a Phase-IIb trial to further validate its efficacy. The ongoing development of novel therapies underscores the complexity of translating basic findings into clinical practice, often presenting more challenges than expected.

Given the success of primate PD models, circuit-specific gene therapy shows a promising future in clinical application. Although AAV-mediated therapies are considered safe and sustainable over a long period of time (Kang et al., 2023), challenges remain in terms of potential immune reactions and unknown long-term effects of chemogenetic manipulation. The cost of medication is another concern for stem cell therapies (Chen & Niu, 2019) and immunotherapies. Currently, available immunotherapies (for other diseases) are expensive, hindering expansion of the market. Regarding the therapy proposed by Chen et al. (2023), the market price is uncertain, but it is hoped that it will be affordable for all patients. Although many factors need to be considered before potential clinical trials, we are enthusiastic about the progress made by the team and hope that their therapy opens the door for a new era in PD therapeutics.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.Q.W., M.Y., and Z.S.G. conceived and wrote the draft. Y.Q.W. generated the figure. All authors read and approved the final version of the manuscript.

Yue-Qi Wang[1,2,3], Ming Yin[1,2,*], Zhe-Shan Guo[1,2,*]

[1] *State Key Laboratory of Digital Medical Engineering*, *School of Biomedical Engineering*, *Hainan University*, *Haikou*, *Hainan* 570228, *China*

[2] *Key Laboratory of Biomedical Engineering of Hainan Province*, *One Health Institute*, *Hainan University*, *Haikou*, *Hainan* 570228, *China*

[3] *Shenzhen Technological Research Center for Primate Translational Medicine*, *Shenzhen-Hong Kong Institute of Brain Science*, *Shenzhen Institute of Advanced Technology*, *Chinese Academy of Sciences*, *Shenzhen*, *Guangdong* 518055 *China*

*Corresponding authors, E-mail: ming_yin@hainanu.edu.cn; guozheshan@hainanu.edu.cn

REFERENCES

Bloem BR, Okun MS, Klein C. 2021. Parkinson's disease. *The Lancet*, **397**(10291): 2284−2303.

Chen YF, Hong ZX, Wang JY, et al. 2023. Circuit-specific gene therapy reverses core symptoms in a primate Parkinson's disease model. *Cell*,doi: 10.1016/j.cell.2023.10.004.

Chen ZZ, Niu YY. 2019. Stem cell therapy for Parkinson's disease using non-human primate models. *Zoological Research*, **40**(5): 349−357.

Kang L, Jin SL, Wang JY, et al. 2023. AAV vectors applied to the treatment of CNS disorders: clinical status and challenges. *Journal of Controlled Release*, **355**: 458−473.

Li H, Su LY, Yang LX, et al. 2021a. A cynomolgus monkey with naturally occurring Parkinson's disease. *National Science Review*, **8**(3): nwaa292.

Li H, Yao YG, Hu XT. 2021b. Biological implications and limitations of a cynomolgus monkey with naturally occurring Parkinson's disease. *Zoological Research*, **42**(2): 138−140.

Roth BL. 2016. DREADDs for neuroscientists. *Neuron*, **89**(4): 683−694.

Volkmann J, Daniels C, Witt K. 2010. Neuropsychiatric effects of subthalamic neurostimulation in Parkinson disease. *Nature Reviews Neurology*, **6**(9): 487−498.

Wang R, Shih LC. 2023. Parkinson's disease - current treatment. *Current Opinion in Neurology*, **36**(4): 302−308.