Title: **Future therapies including CRISPR for Parkinson's disease beyond stem cell**

Author / Authors: Sang Ryong Jeon, Hyung Ho Yoon, Sunghyeok Ye, Justin Lee, Min-Ho Nam, Junseok W. Hur, Seung Eun Lee, Soo-Jin Oh, Kyoungmi Kim

Department of Neurological Surgery, ASAN Medical Center, University of Ulsan SOUTH KOREA

Abstract:
Nowadays, pathophysiology of Parkinson's disease (PD) is being changed as proteinopathy: misfolded a- synuclein accumulation as well as loss of dopaminergic neurons. Therefore, various strategies targeted to these novel findings are being developed in research basis.

Cell replacement therapies, dopaminergic neurons differentiated from embryonic stem cell or iPS are now far advanced, so their efficacy and safety are under evaluation in primates.

Other materials beyond stem cell are shown up recently : control of reactive astrocytes around dopaminergic neurons in substantia nigra, direct transdifferentiation of astrocyte to dopaminergic neuron, graphene resolving aggragated misfolded a-synuclein, and CRISPR to delete mutated gene producing a- synuclein. We utilized CRISPR/Cas9 to delete A53T-SNCA in vitro and in vivo. Adeno-associated virus carrying SaCas9-KKH with a single-guide RNA (sgRNA) targeting A53T-SNCA significantly reduced the A53T-SNCA levels in vitro, without off-target effects on wild-type SNCA. Furthermore, we tested the technique's in vivo therapeutic potential in a viral A53T-SNCA overexpression rat model of PD. Gene deletion of A53T-SNCA significantly prevented the overexpression of α-synuclein, dopaminergic neurodegeneration, and parkinsonian motor symptoms, whereas a negative control without sgRNA did not. Our findings propose CRISPR/Cas9 system as a potential prevention strategy for PD with A53T-SNCA mutation.

Although most of these new strategies are still experimental status, they are novel and can elicit the new era of PD management in near future.