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Long-term intermittent treatment of brain-penetrant LRRK2 inhibitor reduces brain alpha-synuclein oligomers without adverse peripheral effects in LRRK2^{R1441G} mutant mice

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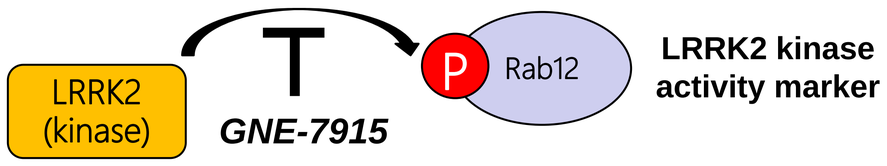
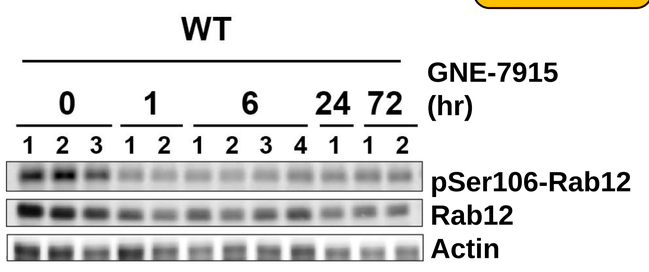
Background

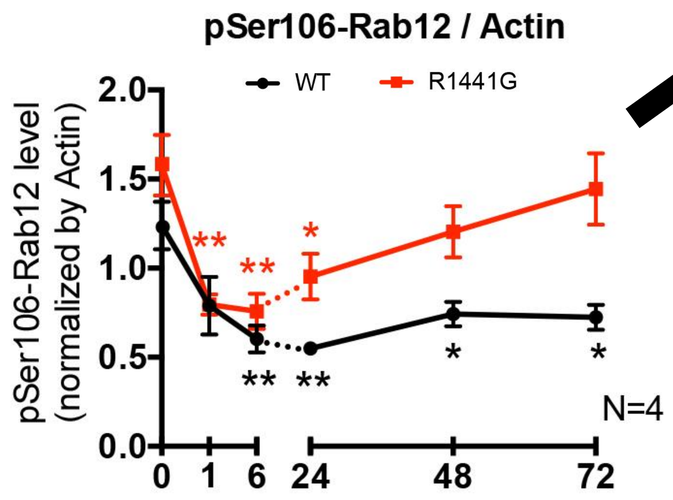
Leucine-rich repeat kinase 2 (LRRK2) mutations which causes autosomal dominant form of Parkinson's disease (PD) displays aberrant hyperkinase activity. Aggregation of misfolded alpha-synuclein in form of Lewy body in the brain is a pathological hallmark of PD, and soluble alpha-synuclein (αSyn) oligomers are cytotoxic. We previously showed that aged LRRK2^{R1441G} knock-in mutant mice developed more αSyn oligomers in the brain than the age-matched wild-type controls. While the efficacy of long-term inhibition of mutant LRRK2 hyperkinase activity on brain αSyn oligomer level in PD remains unexplored, several pharmacological studies on non-human primates have shown adverse side effects in their periphery upon excess LRRK2 inhibition. Here, we first aimed to establish a long-term treatment protocol of a brain-penetrable LRRK2 kinase inhibitor (GNE-7915) injection without excess inhibition of LRRK2 kinase activity. We then aimed to see the therapeutic effect of GNE-7915 on the level of toxic αSyn oligomers in the brain of aged LRRK2^{R1441G} knock-in mutant mice without causing side effects in the periphery.

Drug efficacy of GNE-7915 over different duration based on single-shot injection



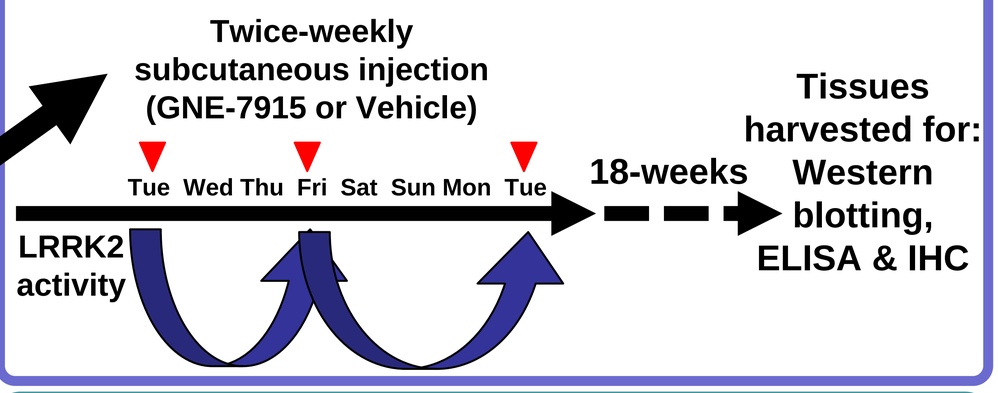
pSer106-Rab12 (Lung)





Single subcutaneous GNE-7915 dose reduced lung LRRK2 kinase activity which dissipated by 72 hr

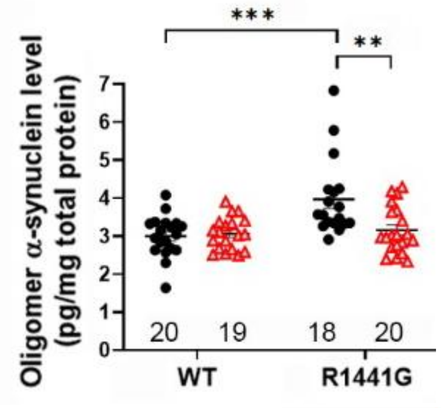
Protocol design for intermittent, long-term GNE-7915 treatment over 18 weeks



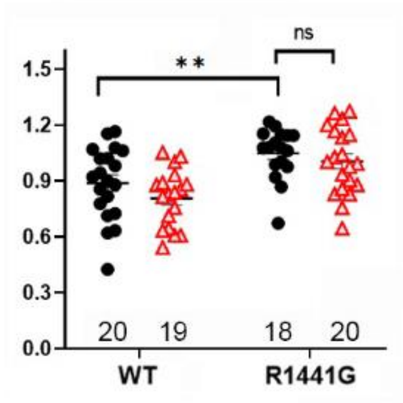
Long-term GNE-7915 injection reduced α-syn oligomer levels in mutant mice brains

(GNE-7915 100mg/kg, s.c., twice-weekly, 18 weeks)

α-synuclein oligomer levels in ***Striatum***



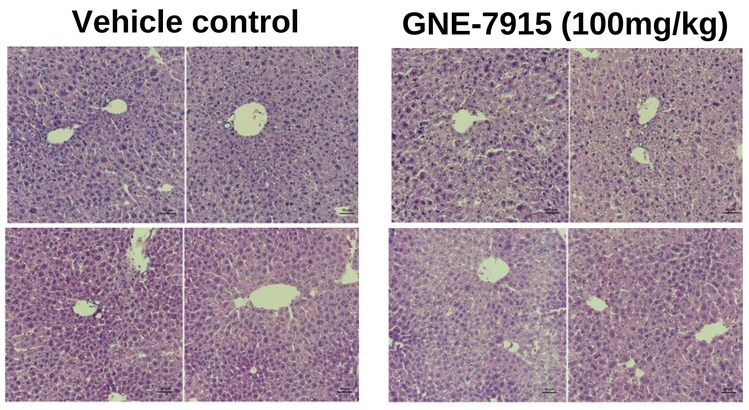
α-synuclein oligomer levels in ***Cortex***



No abnormalities observed in liver and kidney histology

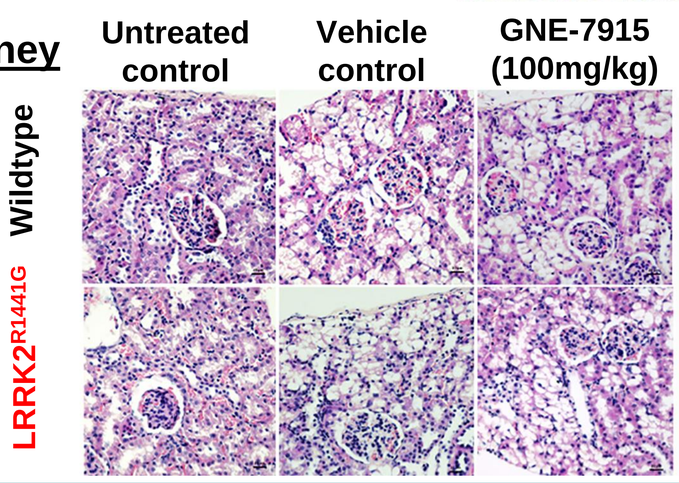
(GNE-7915 100mg/kg, s.c., twice-weekly, 18 weeks)

Liver



Liver histopathology reveals no abnormalities after long-term GNE-7915 treatment (Hematoxylin & Eosin stain)

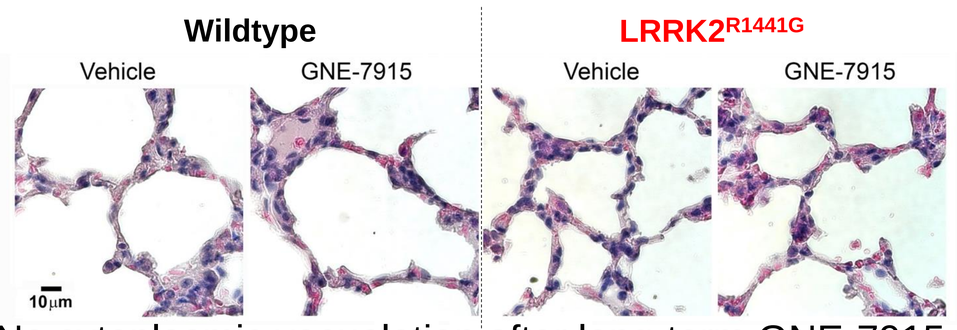
Kidney



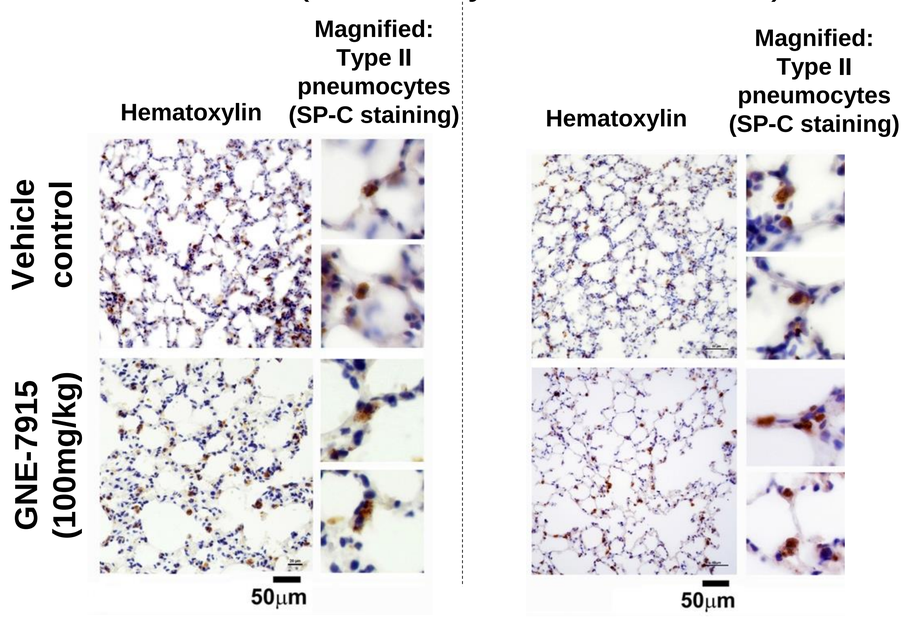
Kidney histology reveals mild renal cortical tubular vacuolation and proliferative glomerulus (caused by the drug vehicle) but no differences between vehicle and GNE-7915 group. (Hematoxylin & Eosin stain)

Absence of abnormal lung histology

(GNE-7915 100mg/kg, s.c., twice-weekly, 18 weeks)



No cytoplasmic vacuolation after long-term GNE-7915 treatment (Hematoxylin & Eosin stain)



IHC of surfactant protein-C (SP-C) reveals no morphological abnormalities in type II pneumocytes of lung (brown = anti-SP-C; counterstain: hematoxylin)

Conclusion

Our 18-week GNE-7915 treatment protocol is effective to reduce accumulation of αSyn oligomers in brains of aged LRRK2^{R1441G} mutant mice without adverse peripheral effects. These results highlight a therapeutic link between LRRK2 kinase inhibition and synucleinopathies of PD, and the importance of kinase inhibitor regimen that minimizes side-effects while preserving therapeutic efficacy.

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