



## Presentation Abstract

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Title: Safe and effective AAV2-mediated expression of NRTN in the substantia nigra supports nigral targeting with CERE-120 in Parkinson's disease

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Abstract: CERE-120 (AAV2-neurturin) is being developed as a treatment for Parkinson's disease (PD). It has been shown to be safe, as well as protect and restore damaged nigrostriatal neurons in animal models of PD. We previously reported results from autopsy tissue, showing that in advanced PD, only limited amounts of neurturin (NRTN) were transported to the cell bodies in the substantia nigra (SN) following CERE-120 administration to, and NRTN expression in the terminal fields in the targeted putamen. Those novel data argued that to be maximally effective for advanced PD, neurotrophic factors should be delivered to both the terminal fields and cell bodies of nigral neurons. We therefore conducted several experiments to study the safety and effectiveness of targeting dopamine cell bodies in the SN. We first injected AAV2-GFP into monkey nigra to quantify distribution of AAV2 vector and establish appropriate SN doses. Using these data, we administered a wide range of CERE-120 doses bilaterally to the SN of rats:  $0.64 \times 10^9$ ,  $3.2 \times 10^9$ ,  $16 \times 10^9$ , and  $120 \times 10^9$  total vg (a dose ~40 times higher than the 'human equivalent' [ $3.2 \times 10^9$  vg], based on relative volumes of SN in rats, monkeys and humans). Also included was an AAV2-GDNF group, using a dose ( $16 \times 10^9$  vg) close to that reported to cause weight loss in rats by

others. A clear dose-related increase in NRTN expression was seen, and as we had projected, the two lower doses limited NRTN expression to an area largely confined to the SN and peri-SN. At higher doses, untargeted NRTN expression occurred well into the diencephalon, as also seen with the AAV-GDNF dose. No behavioral or functional abnormalities or any form of toxicity was seen in any group. The only side effect was a modest reduction in weight gain (max. ~15%), seen only with the AAV-GDNF and highest CERE-120 dose. This reached a maximal effect at 6 wks (of the 13 wk study) and was correlated with a corresponding decrease in food intake. A follow-on study further established that NRTN exposure to SN neurons does not mediate the weight changes. The main group received 6-OHDA 3 wks prior to the highest CERE-120 dose to first destroy the majority of SN neurons. Nonetheless, a comparable effect on weight was seen despite a severely lesioned SN, further implicating mistargeted (non-SN) protein as the culprit. Finally, in another study we demonstrated that the weight effects can be mitigated (by 50%) through simple dietary supplementation of preferred foods (peanut butter, cereal, cookies). Collectively, these data support the conclusion that NRTN expression in the SN can be achieved safely and effectively and provide further empirical support for implementing nigral delivery of CERE-120 in PD patients.

Disclosures:

**R.T. Bartus**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **L. Brown**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **A. Wilson**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **B. Kruegel**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **J. Kordower**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest; **C.D. Herzog**, Ceregene, Inc., Employment; Ceregene, Inc., Ownership Interest.

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