A non-human primate model of Parkinson’s disease based on viral vector mediated overexpression of alpha-synuclein

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Introduction and Aim

- Irrespective of etiology and varying upstream mechanisms, α-syn deposition is a defining pathological feature of PD.
- Rodent models, transgenic mice and AA V rats, have proven useful in better understanding aSyn function, pathology and biochemistry.
- As in vivo platforms for testing efficacy, the rodent models are currently being, or have been, used to evaluate several classes of therapies ranging from immunotherapy, autophagy enhancing, aggregate clearing, etc.
- Currently lacking in the field is a robust, well-characterized non-human primate model based on aSyn overexpression to optimally transition therapeutic development between rodent and human.
- Our aim was to develop a primate model of aSynopathology that could be used to fill this gap in preclinical drug efficacy testing using a species with a proven track record in preclinical drug screening, the cynomolgus macaque.

Materials and Methods

- Animals and viral vector delivery. Female cynomolgus macaques (~9 y, ~3 kg) were injected via MRI-guided stereotaxy with 28 μl of 1.7 x 10^12 AAV1/2 α-syn or a empty vector into the SN over 4 sites within each side of the SN. Behaviour was assessed every month. PET scans (AV-133 and FDG) were conducted every other month.
- Postmortem measures. Animals were perfused with saline 8 months after surgery and brain portions were dissected fresh or post-fixed. Brains were processed for immuno-labeling and HPLC. Double label immunofluorescence was conducted to reveal tyrosine hydroxylase (TH), human α-synuclein or HA to provide detail regarding colocalization. Brightfield microscopy was conducted independently on TH and aSyn stained sections to reveal axonal morphology and to evaluate protein expression. TH stained sections of the SN will be used for stereological estimation of dopamine neuron numbers.

Results

- Distribution of transgene and degenerative changes in the nigrostriatal system produced by exposure to A53T α-synuclein 8 months following injection of AAV1/2
- Reducions in striatal DAT and dopamine neurochemistry following exposure to A53T α-syn
- AV133 VMAT-2 and FDG PET shows changes over time following exposure to A53T α-syn

Summary & Conclusions

1. The model is in a position to assess therapeutics aimed at reducing or preventing aSyn accumulation in the nigrostriatal system in a 4 or 8 month timeframe. Endpoints include: striatal neurochemistry and DAT, aSyn load per DA neuron, striatal aSyn levels, number of TH neurons remaining
2. The model shows a behavioural phenotype that includes reduced locomotor activity in the absence of overt disability, representing a pre-motor phase of the early PD patient
3. Robust aSyn expression throughout the nigrostriatal system allows for proof of concept PET studies to screen potential aSyn ligands