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The following is a summary of the notes made during a verbal presentation by Dino Di Monte at the Syngenta Marlow meeting regarding the preliminary findings from experimental studies with paraquat (PQ) and MPTP in non-human primates (Squirrel monkey). These notes were taken in the presence of Syngenta Legal Council.

Studies have been conducted at the Parkinson's Institute in Sunnyvale, CA on wild caught feral Squirrel monkeys (when questioned the sex and age were not clear).

A single dose of 1.6 mg/kg MPTP (s.c. route) results in a 30% loss of TH⁺ neurones when assessed 1 month post dose. This is a standard model and which has been published previously.

Studies with PQ conducted to replicate the mouse PQ dosing regimen (3 x weekly doses of 5 mg/kg PQ s.c.) resulted in >50% lethality. Loss of striatal dopamine was noted in the dead animals, but this was not quantified.

Further experiments were conducted at a lower PQ dose level of 2.5 mg/kg.

2.5 mg/kg PQ (s.c.) was administered once per week for a total of 6 doses (15 mg/kg total dose) and TH⁺ neuronal cell counts in the substantia nigra *pars compacta* (SNpc) were assessed at 2 or 4 weeks post dose.

No effect of PQ on the number of TH⁺ neurones was observed – this finding is quite different to that observed in the C₅₇Bl₆ mouse where TH⁺ neuronal cell loss (18-28%) has been observed.

Detailed histochemical analysis of the slides showed no change in the total number of TH⁺ neurones compared to control, but did indicate a change in the neuromelanin staining phenotype of some neurones when examined 4 weeks post dose.

This apparent phenotypic change in neuronal staining characteristics is quantified in the table below (numbers were rounded to the nearest 1000 counts). They are believed to be the mean of n ≤ 3 individuals (hence no statistics).

Treatment Group	Total TH⁺ Counts	TH⁺ & Neuromelanin Stain Counts	Neuromelanin Stain Only Counts
Saline Control	61,000	47,000	7,000
PQ 2 weeks	61,000	42,000	6,000

PQ 4 weeks	61,000	37,000	16,000
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The ratio of TH⁺ & neuromelanin staining neurones to neuromelanin only staining neurones changed in the group dosed with PQ and assessed 4 weeks post dose.

An up regulation of alpha-synuclein was also noted in brain samples taken 2, 4 & 8 weeks post PQ dose.

The conclusion Di Monte drew from these experiments was that at the MTD in the Squirrel monkey, PQ did not induce a lesion that resulted in neuronal cell loss in the SNpc (quite different to the mouse model), but that it may induce a change in histochemical phenotype in some of the neuromelanin containing cells. The toxicological significance of this apparent phenotypic change is unclear.

In a separate series of experiments, PQ was administered (2.5 mg/kg once / week for 6 weeks) to Squirrel monkeys. At 4 weeks post dose animals were then exposed to MPTP (1.6 mg/kg single dose - assumed) or saline. Striatal dopamine levels were then assessed 4 weeks post MPTP dose. The initial preliminary findings are represented in the table below. Numbers are assumed to be the mean of a small number (n≤3) of individual animals (hence no statistics).

Treatment Group	Striatal dopamine concentration (unsure of the units?)
Saline Control	167
MPTP alone	56
PQ alone 4 weeks post dose	171
PQ alone 8 weeks post dose	150
PQ 4 weeks + MPTP	141

Exposure to PQ protected against the neurotoxic effects of MPTP.

Di Monte speculated on a possible mechanism that might involve the PQ induced up regulation of alpha-synuclein which is then neuroprotective to a second subsequent insult by the neurotoxicant MPTP.

A similar neuroprotective effect (as measured by striatal dopamine concentrations) of PQ exposure was also observed in the C₅₇Bl₆ mouse model. PQ was dosed once / week for 3 weeks with 5 mg/kg i.p. prior to MPTP (4 x 20mg/kg i.p. in 24 hrs).

Striatal dopamine levels were assessed at 3 & 6 weeks post dose, with the neuroprotective effect at 6 weeks post dose being less robust.

TH⁺ neuronal cell counts in the SNpc are currently being assessed to determine if the apparent protective effect on neurochemical parameters extends to protecting against neuronal cell loss in the mouse.

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