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**MEETING ABSTRACT**

A1.4
Modeling three variants of Parkinson’s in mice based on complex aetiologies in humans
Michael G. SCHLOSSMACHER1*, Julianna J. TOMLINSON1,
Earl G. BROWN1 and David S. PARK2

1Neuroscience Program, The Ottawa Hospital, Univ Ottawa Brain and Mind Research Institute, Ottawa, ON, Canada; 2Department of Cellular and Molecular Medicine; University of Ottawa Brain and Mind Research Institute; Ottawa, ON, Canada

Parkinsonism in humans encompasses several variants. We postulate that the faithful modeling of different subtypes of parkinsonism in mice—based on individual, complex aetiologies observed in humans—is essential in facilitating breakthroughs for cause-directed treatment of our patients. Such breakthroughs will be based on the better understanding of disease processes, related advances in target validation, and the successful development of objective laboratory markers.

Past efforts in replicating Parkinson’s in animals have been disappointing; published models were largely based on either a single genomic change or single neurotoxin exposure. Our team has modeled the complex aetiology for three variants of human parkinsonism in mice. Specifically, we have rebuilt: (1) a complex variant of dominantly inherited disease with motoric and cognitive decline (“synergy mouse”); (2) a multifactorial variant for causing sporadic disease (“reovirus mouse”); and (3) a complex variant to recreate recessively inherited disease (“DJ-1 mouse”).

In pursuing this work, we have incorporated allelic changes at the following genetic loci in our models: In the “synergy mouse”, four copies of a mutant human SNCA allele [1] were combined with knock-in mutations at gba1 [2]; in the “reovirus mouse”, mutant lrrk2 alleles [3] were coupled with exposure to a neurotropic virus [4]; and in the “DJ-1 mouse”, two park7-null alleles were combined with a second hit in the nuclear genome [5]. In carrying out work on all three variants, we have made substantive progress in the modeling of clinically relevant behavioral deficits, biochemical abnormalities, and histological changes; there, we also recorded disease worsening with progression in age. Concrete examples for pathological changes will be reviewed.

We are optimistic that 55 years after Oleh Hornykiewicz and Walther Birkmayer introduced L-DOPA replacement therapy, the better modeling of Parkinson’s variants in laboratory animals, as informed by the complex aetiologies seen in patients, will advance our goal of causal treatment.

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References

*Submitting author e-mail: mschlossmacher@ohri.ca