JOHNS HOPKINS
TECHNOLOGY VENTURES

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Titles & Department

Assistant Director, Human Genetics Graduate Program
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Specialization Area

Applying functional genetics to human neurological/neuropsychiatric/neurobehavioral disease.

Unmet Need

Parkinson disease is the most common movement disorder in the population, and the second most common neurodegenerative disorder. It represents a projected global drug market more than $5B 2021 ($12B by 2031). Treatment modalities have focused on symptom relief. Viable emerging strategies employing Glucagon like receptor agonists display some efficacy if used at the earliest stages of progression; they address the proinflammatory response but not the increasing provocative misfolding of SNCA. The lack of effective treatment modalities facilitates relentless progress and increasing comorbidities, reducing quality of life, depression, including fall injuries, and loss of independence.

Other synucleinopathies include Lewy Body Dementia (LBD) $5B 2021 ($12B by 2031); Frontotemporal Dementia (FTD) $350M in 2022.

Summary of Research & Work

Parkinson disease and associated synucleinopathies present as insidious, chronic, and progressive disorders for which therapies have largely focused on symptomatic relief. Although driven by a combination of genetic and environmental factors, the misfolding and aggregation of alpha-synuclein (SNCA) into insoluble aggregates represents a rate-limiting step in PD pathological progression. Our work focuses on strategies to modulate cell-directed regulatory control of SNCA in PD vulnerable neurons.

Value Proposition

- Dr. McCallion's lab has engineered a catecholamine-neuron-dependent transcriptional regulatory sequence (within the large fourth intron of SNCA) in mice, demonstrating cell-specific reduction in Snca within midbrain dopamine neurons (amongst others).
- They are currently testing the capacity of this engineered mouse line to resist the genetic and environmental induction of PD pathology and progression.
- The mouse line is a unique model system in which to evaluate the need of SNCA in PD vulnerable neurons for all relevant clinical symptoms, including motor and behavioral phenotypes, depression, anosmia, sleep loss, and GI/urinary dysfunction.
- They are beginning to test the capacity of CRISPRi against this regulatory sequence as a potential therapeutic avenue to delay phenotypic onset and slow progression.
- They initially plan to evaluate delivery by stereotaxis, and by nanoparticle transport across the blood brain barrier.

Recent Publications

- McClymont SA, Hook PW, Soto AI, Reed X, Law WD, Kerans SJ, Waite EL, Briceno NJ, Thole JF, Heckman MG, Diehl NN, Wszolek ZK, Moore CD, Zhu H, Akiyama JA, Dickel DE, Visel A, Pennacchio LA, Ross OA, Beer MA, McCallion AS. Parkinson-Associated SNCA Enhancer Variants Revealed by Open Chromatin in Mouse Dopamine Neurons. Am J Hum Genet. 2018 Dec 6;103(6):874-892. doi: 10.1016/j.ajhg.2018.10.018. Epub 2018 Nov 29. PMID: 30503521
- There is unpublished data demonstrating the cell specific reduction in SNCA within dopamine neurons of the ventral midbrain of our engineered mice.

Awards & Honors

- Faculty of 1000, Genomics and Genetics