Development of a neuroinflammatory systems biology platform to enable discovery of disease-modifying therapeutics for Alzheimer’s disease

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ABSTRACT

The presence of neuroinflammation is a pathological hallmark of multiple CNS degenerative diseases. DRiK2 and transcriptomic studies identified microglial dysfunction as a key driver of the chronic neuroinflammation associated with Alzheimer’s disease. Characterization of the non-encephalitogenic cell function of microglia during CNS development revealed the requirement of neuro-glial interactions for normal brain function. These insights provide potential therapeutic strategies whereby adult microglial function is modulated to protect the aging brain. In vitro assays fail to model the complex CNS biology present in vivo, including authentic neuron-microglial interactions and aspects of human aging. Tiaki Therapeutics has developed a systems biology platform that models the neuroinflammatory aspect of Alzheimer’s disease and other neurodegenerative disorders. An integral part of Tiaki’s system is an adult ex vivo brain slice assay, which permits the longitudinal analysis of all CNS cell types within their authentic matrix and inter-cellular environment. Transcriptomes were obtained for whole tissue and isolated microglia to establish the neuroinflammatory signature of the platform. Following an initial period of dynamic changes in gene expression, the Tiaki platform exhibits a stable neuroinflammatory state that can be monitored by transcriptomic and protein analyses. Using a bioinformatics approach, the gene expression signature observed in the adult ex vivo brain slice assay significantly correlates to gene expression data from Alzheimer’s patients. Tiaki’s assay is uniquely positioned to provide longitudinal transcriptomic and proteomic signatures for CNS health and disease, as well as biomarkers for target engagement and compound efficacy. To date we have screened chemical matter for a number of targets in our platform and have been able to identify targets that mitigate the inflammatory signature. Our model of the chronic inflammation associated with Alzheimer’s disease enables the discovery and development of novel targets that demonstrate benefit to surviving neurons.

BACKGROUND

Neuroinflammation: A Critical Driver of Cognitive Decline in AD

Alzheimer’s Disease (AD) Pathology Without Dementia (PWD)

Disease Pathology (plaques)

Microglia staining

Tiaki targets eliminate inflammation and restore cognitive function

Patients with AD/dementia exhibit significant numbers of microglia with activated morphology surrounding Aβ plaques

Tiaki Systems Biology Platform Reveals Novel Targets for Neuroinflammatory AD

Tiaki systems biology platform contains all relevant cell types in their native environment in a state that models neuroinflammatory AD

RESULTS

Tiaki Ex Vivo Platform Models Human AD

• Differential expression (DE) analysis of RNASeq data from postmortem, cognitively normal controls and pathology confirmed AD human brain tissue (data transformed)
• Significant correlation between DE of AD patients and Tiaki system comparing orthologous differentially expressed genes
• Pheotipic reference treatment tested in Tiaki platform demonstrates the system can be modulated to reverse the human AD disease signature

CONCLUSIONS

• Tiaki has created a systems biology platform that models the transcriptomic signature observed in patients with Alzheimer’s disease.
• The disease signature is reversible, indicating the platform is suitable for use in target identification and validation efforts.
• The disease signature can be reversed by pharmacological agents that interfere with the normal function of distinct targets that lie in different functional pathways.
• Target A is in active drug discovery, with initial clinical tests anticipated in 2021.

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