**ABSTRACT**

Neuroinflammation is a pathological hallmark of multiple CNS degenerative diseases. Microglia are the resident CNS innate immune cells and therefore key contributors to this pathology. Many GWAS and transcriptomic studies have identified microglial dysfunction as a key driver of the chronic neurodegeneration that is associated with multiple neurodegenerative diseases, including Alzheimer’s disease. The elucidation of non-invasive immune cell functions of microglia during CNS development has revealed the requirement of neuroglial interactions for normal, healthy brain function. These newly appreciated functions of microglia in CNS health led to the hypothesis that modulation of adult microglial function in CNS inflammatory diseases may be a potential therapeutic strategy to protect the aging, diseased brain. One challenge in the field of neuroinflammation is the ability to authentically model the complex CNS biology present in vivo. This includes critical neuron-glia interactions and aspects of human aging. Tiaki Therapeutics has developed a systems biology platform to enable target identification, target validation, and patient stratification. This platform was used to longitudinally characterize an adult CNS slice model with all intrinsic cell types in their native environment. Analysis of AD and PWD patient cortical samples demonstrated significant differential expression of genes involved in neuroinflammation.**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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