Novel 3D brain tissue-based screening assay for targeting microglia in CNS neurodegeneration

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Research Abstract

Aspects of microglial activation in neuroinflammation associated with CNS neurodegeneration have alternately been reported to be further damaging or to be protective against disease progression. Thus, the translational potential of targeting microglia in new drug development for CNS neurodegenerative diseases remains uncertain. A major challenge in this context has been

that relevant microglial phenotypes and activation states have been exceedingly difficult to recapitulate in cell line models or even in primary cultures of microglia. Conversely, microglial studies in vivo are time- and cost-intensive, and consequently have limited scalability. To address this need, we propose to develop and provide validation for a novel, brain tissue- based drug discovery model for the identification and mechanistic evaluation of new drug and drug target candidates for modulating microglial activation in CNS neurodegenerative disorders. Brain tissue models capture important aspects of intercellular interactions within the intact, local 3-dimensional structure of native neural tissues, and thereby have increased physiological relevance and can be more predictive of clinical benefit compared to cell-based models. Moreover, we have shown previously that brain slice assays can be scaled to useful throughputs for drug discovery in Huntington's disease (HD), Alzheimer's disease (AD), and stroke. The goal of the present proposal is thus to establish the experimental framework for a brain slice-based screening and mechanistic assay for microglial-neuronal interactions, and to provide initial validation that perturbation of microglial activation and/or numbers leads to clear and reproducible effects on rates and/or extents of neurodegeneration. In addition, we will extend the assay to interrogate potential effects of peripheral monocytes, whose infiltration is associated with later stages of CNS disease. We will initially focus on an HD brain slice model that we have used extensively in both screening as well as mechanistic studies, and then ask if our findings are generalizable to different models of CNS neurodegeneration driven by amyloid precursor protein and tau isoforms relevant to AD and frontotemporal dementias (FTD), respectively. If successful, the proposed studies should provide a new 3-D brain tissue-based model for capturing clinically relevant microglial-neuronal interactions scalable to screening throughputs for the discovery of new candidate drugs and drug targets for CNS neurodegeneration, and for their mechanistic evaluation and validation.

Further information available at:

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