Brain Diseases

AMYOTROPHIC LATERAL SCLEROSIS

Background

ALS is a fatal neurodegenerative disease that is characterized by a progressive, selective loss of motor neurons (MN) in brain and spinal cord. The mechanisms of selective and age-dependent MN degeneration in ALS have not been defined. Recent studies suggest that both the sustained glutamate excitotoxicity as well as chronic hypoxic conditions results in increased intracellular oxidative toxicity which contributes to death of MN. The molecular pathways remain largely unknown.

Pathology Model

Compounds will be administered to a well-established motor neuron cell line (NSC-34) differentiated into motor neurons by exposure to Retinoic acid and low serum levels for 4 days as reported in literature . NSC-34 is produced by fusion of motor neuron enriched, embryonic mouse spinal cord cells with mouse neuroblastoma. These cells express many properties of motor neurons, including choline acetyltransferase, acetylcholine synthesis, storage and release and neurofilament triplet proteins. Moreover, NSC34 spinal cord motor neurons expresses glutamate receptor proteins and generate action potentials. NSC34 neurons have been widely used to study mechanisms of neuron signalling and neuron degeneration.

Cells will be challenged with high glutamate concentrations (2-10mM) in the presence of compounds (concentrations will be jointly decided with the Client).

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Readouts

Following stimulation, cells will be quantitatively assayed for the following parameters:

- Quantitative evaluation of cell viability
- Quantitative evaluation of mitochondrial damage
- Quantitative evaluation of caspase 3 activation
- Quantitative evaluation of neurofilament phosphorylation by in-cell western analysis