Modulation of protein accumulation in motor neurone disease

THE EXISTING PROBLEM OR ISSUE
Motor neurone disease (MND) and frontotemporal dementia (FTD) are devastating neurodegenerative diseases that are currently untreatable.

Genetic studies have revealed causative mutations in the TDP43 gene for both diseases. As a result, ubiquitylated TDP43 proteins aggregate in neurons and are considered the hallmark pathology of these diseases.

The formation of TDP-43 aggregates are believed to be an underlying event leading to the neurodegeneration that causes MND and FTD, either because the TDP-43 aggregates themselves are neurotoxic or they cause loss-of-function of TDP-43. The mechanism behind the formation of this common pathological characteristic is unknown, but abnormal ubiquitylation of TDP-43 appears to be of critical importance.

Animal model studies have shown TDP43 inclusions cause MND-related symptoms in transgenic mice. Therefore strategies to prevent or clear the formation of TDP43 aggregate are currently a major target for therapeutic intervention.

OUR SOLUTION
We have identified the first disease-associated E3 ubiquitin ligase (Cyclin F) that directly targets TDP43 for ubiquitylation.

It is believed that abnormal ubiquitination of TDP-43 contributes to its aggregation, and accordingly we find that disease-causing mutations in Cyclin F cause hyperubiquitylation of TDP-43 and neuronal death.

Therefore we believe that over-expressing Cyclin F can prevent or slow down disease progression by modifying the function of TDP-43.

APPLICATIONS
- Delivery of cyclin-F to neurons
- Manipulating cyclin-F expression in neurons to correct the ubiquitylation status of TDP43.
- Manipulating cyclin-F expression in neurons to improve the clearance of TDP43.

INVENTORS
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INTELLECTUAL PROPERTY POSITION
Patent Application
Modulation of protein accumulation and uses therefor

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BENEFITS
Endogenous method for directly controlling TDP-43 ubiquitylation

ADVANTAGES
Can utilise an endogenous pathway within neurons (i.e: does not introduce off-target side-effects).

Experts in role of Cyclin F in MND/FTD
We were the first group to identify disease-causing mutations in Cyclin F in MND and FTD patients. We have all of the research tools required to develop this technology further.

Viral-mediated overexpression of cyclin F in mice is safe
We have validated that this approach is safe