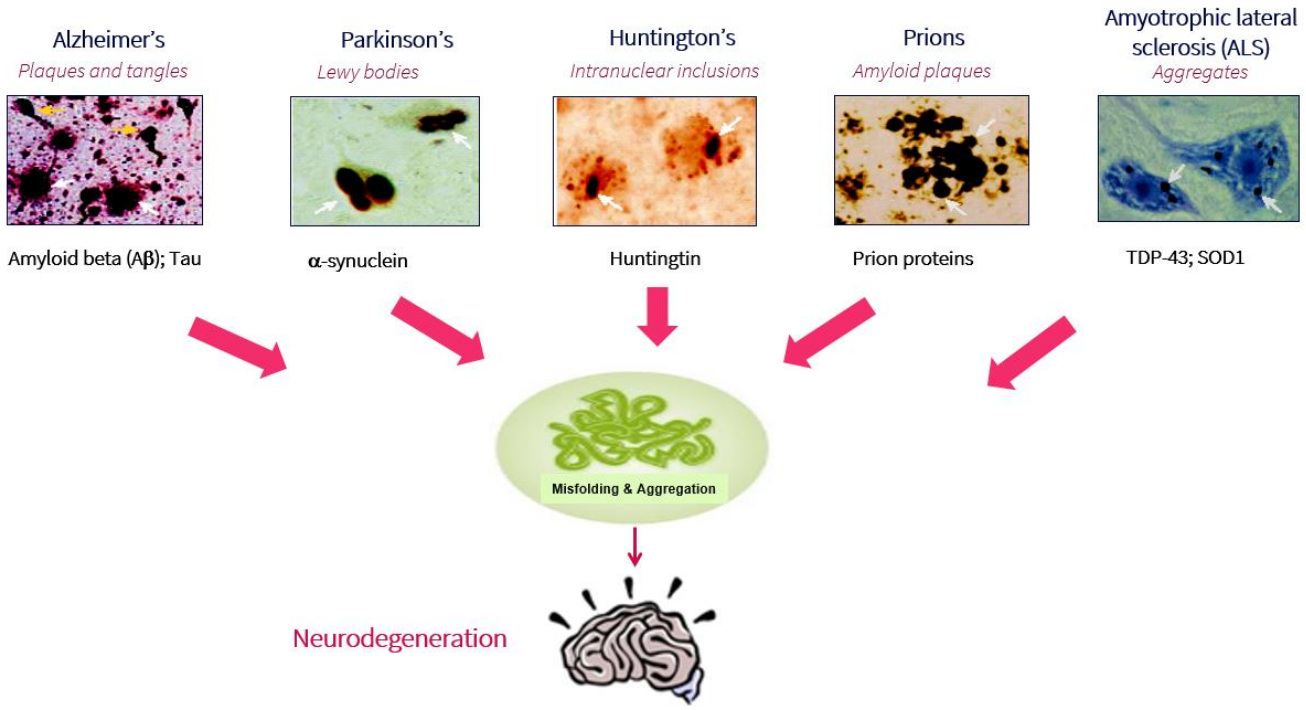
e-therapeutics

Network-driven Drug Discovery

MODULATION OF PROTEOSTASIS IN NEURODEGENERATIVE DISEASES

BACKGROUND

Many Neurodegenerative Diseases are Characterized by the Presence of Disease-specific Misfolded Proteins



There have been a number of high profile failures of therapeutics targeting disease-specific misfolded proteins, most notably amyloid beta (Aβ)-targeting therapies for Alzheimer's disease. Targeting processes occurring downstream of protein misfolding may be more rewarding than targeting individual aberrant proteins. One such process is the unfolded protein response (UPR), an important quality control mechanism which is activated if protein folding homeostasis of the ER is disturbed. Markers of UPR activation have been found in the brains of patients with various neuropathological diseases.

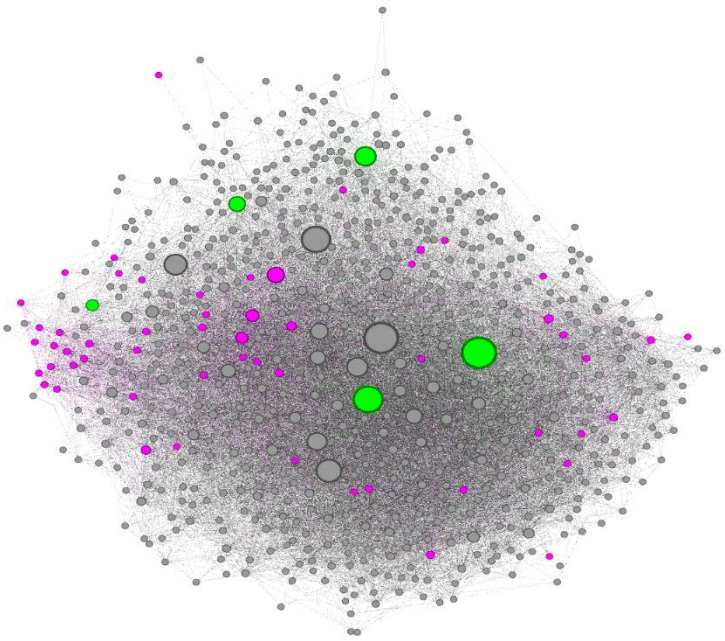
The PERK kinase arm of the unfolded protein response has been particularly implicated in neurodegenerative disease pathogenesis. Sustained activation of this process leads to a catastrophic decline in key neuronal proteins, resulting in neuronal loss. Studies have shown that inhibitors of PERK, are therapeutically effective in models of neurodegenerative disease. However, these inhibitors caused on-target side effects on the pancreas. Compounds affecting the appropriate biological process, but without directly targeting this particular protein may be efficacious against neurodegenerative diseases, but without the toxicity associated with PERK inhibitors.

As UPR activation has been implicated in many protein misfolding neurodegenerative diseases and is not a process focused on individual disease-specific proteins, there is potential for a therapeutic strategy that could be beneficial across a spectrum of neurodegenerative diseases.

THE APPROACH

Network-driven Drug Discovery

Network models representing translational repression mediated via the UPR can be constructed using a variety of techniques. These networks can be analysed using our proprietary analytics, producing lists of compounds predicted to perturb UPR, and to potentially have therapeutic benefit in a number of neurodegenerative diseases.



Example network based on UPR
Green nodes = seed proteins
Pink Nodes = Proteins important to translational suppression in response to stress

THE OPPORTUNITY

e-therapeutics' platform can be used in diverse therapeutic areas to identify novel and differentiated hits for subsequent hit-to-lead and lead optimisation.

Neurodegenerative diseases are increasing in prevalence, with no curative therapies currently available. e-therapeutics' **Network-driven Drug Discovery** platform may be used to identify small-molecules that can be tested for their effects on the unfolded protein response and in subsequently in *models of* neurodegenerative diseases.

Please Contact
Dr Ray Barlow, CEO
T +44(0)7387411612
ray.barlow@etherapeutics.co.uk

e-therapeutics

Network-driven Drug Discovery

17 Blenheim Office Park
Long Hanborough
Oxfordshire, UK