Preclinical Evaluation of a Novel Neurotherapeutic for ALS

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Grant: 65 000 €

There is an urgent need for effective drugs to treat ALS. Due to the complexity of biological pathways involved in ALS, it is now thought that drugs that work at many different levels may offer distinct advantages over drugs targeting only one pathway.

Thyrotropin-releasing hormone (TRH) occurs naturally in humans and works on many different biological pathways within the central nervous system. Until now, the medical use of TRH has been limited by its rapid degradation.

A novel lead compound (LC) has now been developed that overcomes this constraint. LC, discovered by the Principal Investigator through Wellcome Trust-funded research, is a first-in-class compound designed to potentiate well-documented multifactorial neurotherapeutic effects of the naturally-occurring neuropeptide TRH, which are recognised to be advantageous in treating CNS disorders, therapeutically beneficial in humans, and relevant to ALS. LC has favourable physicochemical and neuropharmacological properties and a clean safety profile; moreover, preclinical studies show LC provides significant functional neuroprotection in two distinct models of neurodegeneration. In particular, we have recently shown that pre-symptomatic treatment with LC has a strong positive effect in a model of ALS.
We now propose to undertake a translational research project to build upon these encouraging results and progress the preclinical development of LC as a potential novel pharmacological treatment for ALS. The performance of these preclinical studies will increase the possibility of translating positive findings to humans with ALS.

This project brings together a multidisciplinary team of experienced researchers based at Trinity College Dublin, Ireland. The team includes Dr Julie A. Kelly (PI) – a senior researcher with more than 25 years neuroscience research experience and inventor of the novel neurotherapeutic lead compound to be evaluated; Professor Orla Hardiman (co-PI) – a clinician scientist, established international ALS researcher, experience clinical trialist and editor of the ALS journal; Dr Natalie Cole – a postdoctoral research fellow with many years basic research experience in the ALS field; Ms Gillian Slator – an skilled research assistant who has worked on the development of the lead compound with Dr Kelly since 1995. All team members are excited by their recent results that show significant positive effects of the lead compound in a gold-standard model of ALS and all are enthusiastic about advancing this line of research.

PENNA - Preclinical Evaluation of a Novel Neurotherapeutic for ALS

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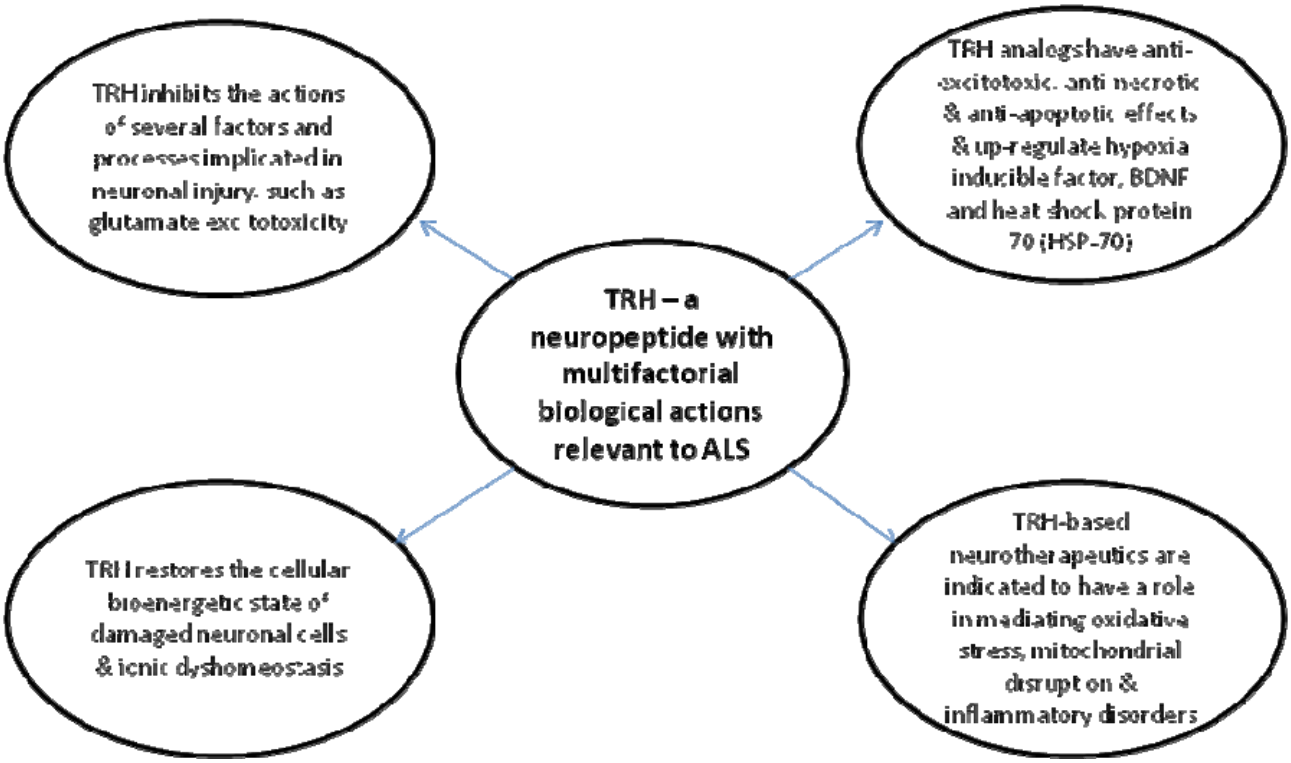
The novel neurotherapeutic that we are evaluating as a prospective treatment for ALS is a compound based on the naturally-occurring neuropeptide thyrotropin-releasing hormone (TRH).

TRH has multiple effects in the central nervous system (CNS) that are recognised to be therapeutically beneficial in treating a wide range of CNS disorders, including ALS (see Figure below). In treating CNS disorders involving multiple pathological mechanisms and cells types, such as ALS, it is now increasingly acknowledged that drugs acting on a range of pathogenic factors may be more efficacious and offer clinical advantages over strategies directed toward a single injury mechanism.

While such an approach might be accomplished by a cocktail of drugs, this tactic could be limited by potential drug interactions, developmental and regulatory challenges and cost. An attractive alternative approach is a single multifunctional therapeutic agent, such as TRH, that modifies multiple pathological mechanisms.

Critically clinical use of TRH has been severely hampered because of its rapid degradation by an enzyme called TRH-degrading ectoenzyme, as well as potential endocrine side-effects increasing the risk of hyperthyroidism. We have developed a novel lead compound (LC) that overcomes these constraints and offers an innovative means to deliver the multifactorial therapeutic effects of naturally occurring TRH.

Our project funded by Fondation Thierry Latran will provide exciting information regarding the ability of LC to (i) provide therapeutic benefit in a model of ALS when given at symptomatic onset, (ii) cross the blood brain barrier, and (iii) modify biologically relevant biomarkers.


TRH – a neuropeptide with multifactorial biological actions relevant to ALS
TRH inhibits the actions of several factors and processes implicated in neuronal injury, such as glutamate excitotoxicity
TRH analogs have anti-excitotoxic, anti necrotic & anti-apoptotic effects & up-regulate hypoxia inducible factor, BDNF and heat shock protein 70 (HSP-70)
TRH restores the cellular bioenergetic state of damaged neuronal cells & ionic dyshomeostasis
TRH-based neurotherapeutics are indicated to have a role in mediating oxidative stress, mitochondrial disruption & inflammatory disorders