Researcher: PROF PERRY BARTLETT
Project: A NOVEL EPHRIN RECEPTOR A4-Fc FUSION PROTEIN FOR THE TREATMENT OF SPORADIC MND

Who are you and where do you work?
Professor Perry F Bartlett, the Founding Director of the Queensland Brain Institute 2003 - 2015, and Foundation Professor in Molecular Neuroscience at the Queensland Brain Institute, The University of Queensland.

Can you give us a summary of your training/experience background?
PhD in Immunology at Melbourne University, Postdoctoral fellow at Johns Hopkins University, USA and University College, London. Head of Neurobiology and Development at the Walter and Eliza Hall Institute. ARC Federation Fellow; NHMRC Senior Principal Research Fellow.

How did you come to work in MND research?
My work in neuronal cell death and motor neuron development first brought me into the MND field.

Can you describe the work your lab is currently pursuing?
We discovered Ephrin A4 (EphA4) was vital for guiding motor neuron's during development to their appropriate targets almost 20 years ago. Since then, we have shown in mature animals that the re-expression of EphA4 on motor neurons following physical damage, or diseases like MND, may prevent recovery and lead to motor neuron cell death. We have shown in animal models of MND that lowering EphA4 levels by genetic or pharmacological means results in significantly longer retention of motor neuron function and delayed cell death.

The last few years have been spent developing effective blockers of EphA4 called mEphA4-Fc, which can be used in humans. We have been successful in developing such a molecule, which is now beginning production. The next phase is to test the effectiveness of this molecule in another animal model, and undertake toxicology studies, with the plan to take it to clinical trial by 2018. We are also working on how EphA4 kills motor neurons using genetic approaches.

How did you identify your drug as a potential treatment for MND?
The findings that lowering levels of EphA4 by genetic or pharmacological means resulted in prolonged retention of motor neuron function in animal models of MND, indicated that blocking EphA4 was a potential therapeutic treatment for MND.

What excites you about this drug(s)?
This molecule has been modified by us to have a long half-life - effective levels are retained in the blood for up to 5 days after injection - while retaining its effective blocking activity, and, in animal studies to date, it appears to have no toxicity.

What difference will the awarding of this grant make to your work?
This grant will allow us to carry-out the remaining animal experiments, toxicology testing, and reagent preparation required to proceed to clinical trials.

THE PROJECT
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The primary objective of the research programme is to complete mEphA4-Fc formulation and nonclinical studies in order to advance mEphA4-Fc to a first-in-human study within the next 2-3 years.

The EphA4 receptor is a key molecule in the repair of damaged motor neurons. It has been implicated in disease progression of MND in preclinical models, while EphA4 mRNA levels isolated from the blood of MND patients correlates with disease progression.

In a genetic ablation EphA4 MND (SOD1) model, mice showed improved motor performance correlating with preservation of lumbar motor neurons compared to wild type controls. Uniquely amongst MND treatments, mEphA4-Fc has the potential to promote axonal regeneration.

We have further engineered a mutant (mEphA4-Fc) fusion protein designed so as to retain the potent activity of the naturally occurring ephrin receptor but with a long systemic half-life well suited to clinical application. A similar molecule has shown improvements in motor function in a mouse MND model and efficacy in neural regeneration following spinal cord injury in mice.

The research programme proposes rapid progression of drug formulation and nonclinical activities, including toxicology studies studying safety of mEphA4-Fc in rodent and non-rodent species. Safety pharmacology studies will also be completed, and important assays developed to characterise mEphA4-Fc pharmacokinetics and monitor drug-related immunogenicity. Once completed we expect to commence human studies and deliver a meaningful benefit to patients suffering from sporadic MND.

FIGHT MND.

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