brainwave

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Next generation invertebrate models for Neurodegeneration

We are looking for a collaboration with a pharmaceutical company to develop and validate new models of neuro-degenerative disease for target validation and compound screening.

Executive Summary

The use of invertebrates to model neurodegenerative disease is well established in an academic context, with a large body of research and examples of successful compound testing (e.g. Sarantseva 2009; Faust K *et al*, 2009; Sherzer-Attali R *et al.*, 2010). Brainwave-Discovery is developing novel Drosophila models of neurodegeneration to target the specific needs of pharmaceutical research and development. The genetic manipulation and phenotyping techniques used in our models have been optimised to study multiple genetic interactions and variants rapidly, cost-effectively and with increased validity to the human condition. Invertebrate models that show evidence of clinical relavance and translation to humans may be used to test the efficacy of compounds for candidate selection and improve understanding of disease processes. If necessary, the information gained from these models can be used to inform the development of the most relevant mammalian models reducing the use of transgenic mice. Our belief is that these models will reduce the requirement for mammalian animal models, yet increase the number of compounds that may be screened, and will help reduce attrition and increase our understanding of disease processes.

Scientific Background

Neurodegenerative diseases such as Alzheimer's and Parkinson's represent major health and financial burdens for society. There are currently no pharmaceutical treatments for these diseases that address the central neurodegeneration process rather than secondary symptoms of nerve cell dysfunction and loss. Mammalian (e.g. rodent and primate) models are currently seen as essential test beds for the development of such treatments. We propose that the use of Drosophila models of human neurodegenerative diseases, as a first stage in system analysis and drug testing, will fast-track research and development and reduce attrition.

Several lines of evidence now indicate that multiple interacting genetic mechanisms underpin disorders of neurodegenera-tion. Drosophila is the ideal first *in vivo* model to study new genetic interactions (i.e. multi-gene models) or new gene variants. The development of humanised fly brain models - with human proteins being used as part of the molecular machinery of the neural nerve cells - enables rapid testing of their role in neurodegeneration and thus their potential as a drug target(s). Use of these models is rapid, cost-effective and relevant, as they are based on human sequence(s).

Current state of the art

The standard approach to neurodegenerative disease modelling is to create transgenic mice expressing mutant forms of human disease-related proteins. This has had varying degrees of success, but currently remains central to validating targets then subsequently assessing efficacy of lead compounds before human testing. Use of Drosophila models as an integral part of the drug development process will allow more wide-ranging, efficient and effective development of therapeutic molecules and reduce transgenic mouse usage.

Current Drosophila based models address single genetic elements. Brainwave-Discovery is proposing a new systems approach bringing together multiple interacting molecular components that will more faithfully model disease mechanisms. The uniqueness of our technology is that we can complement these more complex genetic models with proprietary, high quality neurophysiology and behavioural readouts using automated systems that are optimised to scale rapidly from research validation studies through to deployment in screen situations.

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What could our solution be used for?

The availability of plug-and-play genetic models for neurodegenerative diseases would allow pharmaceutical developers to rapidly assemble large numbers of new, human-relevant, disease models for testing compounds *in vivo* or validating disease mechanisms. The speed and low cost of Drosophila allows a wide variety of models to be developed to determine the effects of specific mutations, up or down-regulation of protein expression or changes in cell localisation. Complex models to study the interactive effects of multiple human proteins on the disease process can be assembled rapidly. These models could be used for target identification and validation, to improve understanding of the underlying mechanisms of disease and also as a disease model to screen compounds for efficacy. They could also be used to predict whether a transgenic mouse model would be of clinical relevance prior to its development.
This approach can also be applied to other areas of CNS drug development such as cognition, migraine and epilepsy. The gains here are two fold: first, more early stage lead compounds can be tested in the Drosophila model as it is cheaper and faster than current systems and second, animal use would be reduced as only the best compounds validated in the fly screen would be taken into mammal studies.

Need for collaboration

We are seeking an active collaborator with whom we can select an appropriate disease model to develop. Our ideal model would be one with a small number of genetic components which we would humanise. At least one of these components would have several genetic variants that may be linked to disease mechanism or drug efficacy. We would look to characterise the genetic strains as well as perform a validation compound screen.

The project is likely to take around 12-18 months depending on the specifics. We expect to provide half the project costs from a combination of in-kind and cash contributions ourselves to be met with a similar contribution from our partner.

3Rs impact assessment

Drosophila is an elegant intermediate step linking the current high throughput *in vitro* screening systems with mammalian *in vivo* assays. Generally, transgenic mice are used to better understand disease processes, and to identify and validate drug targets. Drosophila models that show evidence of clinical validity and translation to humans may be used to reduce the use of animals by:

i) providing information that would currently be gained using transgenic mice
ii) preventing the development of transgenic mice that may not be relevant to human disease
iii) avoiding compounds that may fail later in development from being taken into animals

Keywords

Neurodegeneration, invertebrate, target, compound, mechanism, replacement, synthetic biology, systems biology, Drosophila, Alzheimer's, Parkinson's

To find out more or to connect with the technology developer contact: crackitenquiries@nc3rs.org.uk