Identification and Cross-validation of Early Stage Phenotypes in Mouse Models of Huntington's disease

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Title of project or programme

Title of PI	Identification and Cross-validation of Early Stage Phenotypes in Mouse Models of Huntington's disease

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

848701.20

Start date of award

14-04-2009

Total duration of award in months

36

The project/programme is most relevant to

- Huntington's disease

Keywords
Research abstract in English

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder with a mean age of

onset of 40 years. Symptoms include motor disorders, psychiatric disturbances, cognitive decline and weight loss, disease duration is approximately 15-20 years and death occurs from co-morbid events. Effective symptomatic therapy is available for some psychiatric symptoms, but treatment of the motor disorder is challenging and there are no therapies that halt or slow the cognitive decline or disease progression. The combination of a slowly progressive disease of variable presentation with a poor battery of assessment tools has meant that phase III clinical efficacy trials performed to date have been underpowered. To remedy this situation, the European Huntington's Disease Network (EHDN) (funded by the CHDI Foundation) has been established to provide the infrastructure, tools and resources necessary to perform clinical trials for HD in Europe. Because HD is an autosomal dominant disease with a genetic diagnostic test, virtually all individuals in the ultimate HD target group, those with premanifest or early stage disease, can be determined with certainly. To develop the assessment tools to monitor the emergence and progression of disease in this group, the CHDI Foundation has funded TRACK-HD, a three year initiative that commenced in 2007 to identify and compare head-to-head clinical, imaging and wet biomarker assessment tools.

The molecular pathogenesis of HD is extremely complex and many potential therapeutic targets have been proposed. However, because clinical efficacy trials will remain resource intensive and expensive, the number of compounds that can be tested in the clinic will inevitably be limited. The demonstration that a therapeutic strategy has disease modifying effects when administered to HD mouse models is the factor most likely to influence the prioritisation of compounds entering the clinical. Therefore, preclinical efficacy trials must be as rigorous, controlled and reproducible as possible and ideally will incorporate clinically cross-validated outcome measures. In partnership with the CHDI Foundation, this proposal will conduct a detailed comparative evaluation of HD mouse models, with a particular focus on presymptomatic and early stage disease using outcome measures chosen to complement the TRACK-HD clinical study. It aims to inform the design of preclinical assessment trials and to match the choice of outcome measures to those that will emerge as being the most useful for clinical evaluation. This synergy will maximise the chance of translating successful therapeutic strategies for HD into the clinic using validated HD mouse models.

Lay summary
In which category does this research fall?

- Basic research