within the first exon of the HD gene. This mutation leads to an elongated glutamine (Q) repeat within the huntingtin protein (Htt), giving rise to a toxic gain of function of the protein. Mutant Htt also forms intracellular inclusions but the pathogenic role of these inclusions is under debate. Current HD therapies available to patients do not target the mutant protein directly but only alleviate symptoms. One possible way to treat HD at the protein level involves the use of VHH. VHH consist of the epitope recognizing domain of a unique heavy chain only antibody class found in camelids and sharks. Apart from their small size (16 kDa), VHH are thermostable, easy to produce and despite their single domain nature VHH have comparable affinities for their antigen as conventional antibody molecules. Furthermore, they can be expressed intracellularly to modulate or detect its target inside a living cell.

**Aim** Identify VHH that bind to mutant Htt, inhibiting its toxic function, thus alleviating HD pathogenesis.

**Results** VHH were selected from a llama phage display library originating from llama (*Llama Glama*) immunised with an N terminal fragment consisting of the first 550 amino acids of the Htt protein with an elongated repeat (Q44). Selection was performed using a smaller N terminal fragment (amino acids 14 to 378) with either a normal repeat (Q17) or an elongated repeat (Q43). Binding by the selected VHH of the N terminal Htt fragment was tested using ELISA, Western blot and immunohistochemistry. Selection resulted in 13 different VHH that were specific for the N terminal Htt fragment. There was no apparent difference in binding efficiency of the VHH to the normal fragment and the fragment with the elongated Q repeat.

**Conclusion** The immunised llama phage display library was successfully used to select VHH specific for the N terminal part of the Htt protein. Promising VHH will be transfected into a cell model of HD to monitor their effect on HD pathogenesis.

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**B11** TARGETING THE NRF2 PATHWAY IN HUNTINGTON’S DISEASE: FUMARIC ACID ESTERS AS A NEW THERAPEUTIC OPTION IN NEURODEGENERATION?

**doi:** 10.1136/jnnp.2010.222596.11

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**Objective** To investigate the therapeutic efficacy of the fumaric acid ester dimethyl fumarate (DMF) in mouse models of Huntington’s disease (HD).

**Background** The exact sequel of events finally resulting in HD neurodegeneration is only partially understood and there is no established protective treatment so far. Besides immunomodulatory actions and efficacy as disease modifying therapy for multiple sclerosis, DMF potentially exerts neuroprotective effects via induction of ‘nuclear factor E2-related factor 2’ (Nrf2) and detoxification pathways. Thus we investigate the therapeutic efficacy of DMF in the R6/2 and YAC128 mouse model of HD.

**Methods** 3-5-week-old R6/2 (*n*=25) and YAC128 mice (*n*=45) were treated with 0.5 mg DMF orally twice a day or vehicle only. Motor performance was assessed monthly using an accelerating rotarod and graded with a clamping score. Histological analyses of R6/2 mice included immunohistochemistry for Nrf2, huntingtin, microglial activation markers and confocal laser scanning microscopy for NeuN/Nrf2 and GFAP/Nrf2. Neuronal loss was quantified after NeuN and cresyl violet staining.

**Results** Treatment with DMF significantly prevented weight loss in R6/2 mice between postnatal days 70 and 80 (*p*<0.0001). At the same time, DMF treatment led to an attenuated motor impairment as measured by the clamping score (0.33±0.15 vs 1.37±0.24, *p*<0.05). Average survival in the DMF group was 102.3 days versus 97.9 days in the placebo group (*p*=0.05). Quantification of neuronal densities revealed a significant preservation of intact neurons in the striatum and motor cortex. These results in R6/2 mice were corroborated in a YAC128 cohort where DMF treatment also led to an attenuated motor impairment.

**Conclusion** In HD mouse models, DMF may exert some beneficial clinical effects and preserves intact neurons. Given its excellent side effect profile, further studies with DMF as a potential neuroprotective approach are warranted in this paradigm.

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**B12** TREATMENT WITH ARIMOCLOMOL DOES NOT LEAD TO RESCUE OF MOTOR OR STRIATAL DEFICITS IN THE YAC128 MOUSE MODEL OF HUNTINGTON’S DISEASE

**doi:** 10.1136/jnnp.2010.222596.12

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**Background** Huntington’s Disease (HD) is an inherited neurological disorder characterised by loss of motor coordination, cognitive dysfunction and psychiatric disturbances that remains without a cure. Arimoclomol, a compound reported to enhance cellular stress induced heat shock protein response, has been shown to be neuroprotective in a mouse model of amyotrophic lateral sclerosis (ALS).

**Aims** To examine whether treatment with arimoclomol would (a) protect against quinolinic acid (QA) mediated excitotoxicity and (b) improve the phenotype of the YAC128 mouse model of HD.

**Methods** 3 month old wild-type (WT) mice were pretreated with PBS or arimoclomol (40 mg/kg, intraperitoneally) followed by an intrastriatal injection of QA (20 nmol) 30 min later. Striatal lesion volume in arimoclomol and PBS treated animals was assessed 7 days later. YAC128 and WT mice were treated with 80 mg/kg of arimoclomol administered in the drinking water for 10 months, starting at 2 months of age. YAC128 and WT animals receiving water only served as no treatment controls. Motor function was assessed using the accelerating and fixed speed rotarod tests at 2, 4, 6, 8, 10 and 12 months of age. Striatal pathology was assessed using unbiased stereology at 12 months of age.

**Results** In animals that received intrastraital injections of QA, there was no significant difference in lesion volume between those pretreated with arimoclomol compared with those treated with PBS only. In animals receiving arimoclomol chronically, there was no significant difference between arimoclomol treated and untreated WT animals in motor performance, as assessed by the accelerating and fixed speed rotarod tests. The motor performance of untreated YAC128 HD mice was significantly lower compared with that of untreated WT animals. Treatment with arimoclomol had no effect on motor performance of YAC128 HD animals compared with untreated YAC128 HD animals. Further, brain weight and striatal volume of untreated YAC128 HD animals was significantly lower compared with untreated WT animals. Treatment with arimoclomol had no effect on brain weight or striatal volume of YAC128 HD animals compared with untreated YAC128 HD mice.

**Conclusions** Our findings demonstrate that treatment with arimoclomol does not lead to improvements in motor function or rescue of striatal pathology in YAC128 HD mice.
B12 Treatment with arimoclomol does not lead to rescue of motor or striatal deficits in the YAC128 mouse model of Huntington’s disease

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J Neurol Neurosurg Psychiatry 2010 81: A14
doi: 10.1136/jnnp.2010.222596.12

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