# Characterising Kynurenine 3-Monooxygenase (KMO) As A Therapeutic Target For Huntington’s Disease

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**Country**

United Kingdom

**Title of project or programme**

Characterising Kynurenine 3-Monooxygenase (KMO) As A Therapeutic Target For Huntington's Disease

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MRC

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€ 1,091,007

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01/12/2015

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3.0

**The project/programme is most relevant to:**

Huntington's disease

**Keywords**
**Research Abstract**
Huntington’s disease (HD) is an incurable, fatal neurodegenerative disorder caused by the expansion of a polyglutamine tract in the huntingtin protein. A hallmark of HD is the perturbation

of the kynurenine pathway (KP), such that there is an increase in neurotoxic metabolites (quinolinic acid; 3-hydroxykynurenine) relative to the neuroprotective metabolite (KYNA). The KP enzyme kynurenine 3-monooxygenase (KMO) plays a central role in the regulation of this pathway; indeed its inhibition leads to normalization of the pathway in HD models, and a shift towards neuroprotection. We have found that pharmacological KMO inhibition also ameliorates neurodegeneration and other disease-relevant phenotypes in models of HD, including fruit flies and mice, making KMO inhibition a promising candidate therapeutic strategy. Notably, KMO inhibition specifically in the blood of HD mice is efficacious, but it is not yet known whether inhibition in the CNS yields similar or enhanced levels of neuroprotection. Here we propose to validate KMO inhibition as a therapeutic strategy for HD by a number of approaches. We will employ our recently developed KMO conditional knockout mice, which will be crossed to R6/2 mice to test the efficacy of KMO inhibition by genetic means. We will delete KMO either globally, or specifically in the periphery or CNS in order to dissect the differential effects of KMO inhibition in these regions. We will expand upon this work by testing KMO inhibition in myeloid cells derived from HD patients. In parallel with this work, we will employ genomics approaches to explore the biology underlying KMO inhibition in control and HD mice, as well as in myeloid cells from HD patients. Finally, we will explore the biological relevance of our preliminary findings that KMO and huntingtin interact physically at mitochondria. In total, this work will clarify the therapeutic relevance of KMO inhibition in HD, which – if promising – will help translation to the clinic.

**Lay Summary**
**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United Kingdom

**Diseases:**
Huntington's disease

**Years:**
2016

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