

Team makes breakthrough in search for neurodegenerative disease treatments

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A significant breakthrough has been made by scientists at The University of Manchester towards developing an effective treatment for neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's.

Researchers at the Manchester Institute of Biotechnology have detailed how an enzyme in the brain interacts with an exciting drug-like lead compound for Huntington's Disease to inhibit its activity. Their findings demonstrate that it can be developed as an effective treatment for [neurodegenerative diseases](#). The research is published in the journal *Nature*.

Working with colleagues at the University of Leicester and the University of Lisbon in Portugal, the researchers identified the molecular structure of the enzyme kynurenine 3-monooxygenase (KMO), which is found in the [human brain](#). It took five years for the team to establish the crystal structure of KMO – the first time it's ever been done.

The scientists then studied how the compound UPF 648 binds incredibly tightly to the enzyme to act as an inhibitor. Previous studies with animal models of neurodegenerative disease have showed that switching off the [enzyme activity](#) through drug binding should be effective in the treatment of [brain disorders](#).

Professor Nigel Scrutton who led the study said: "UPF 648 works very

well as an inhibitor of enzyme activity. However, in its current form it does not pass into the brain from the blood. The search is now on for related compounds that can both inhibit the enzyme and pass into the brain."

He continues: "Our research detailing the [molecular structure](#) of the enzyme now enables a search for new KMO inhibitors that are able to cross the blood-brain barrier. This provides real hope for developing [drug therapies](#) to target neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's diseases."

Dr Flaviano Giorgini, the team's neurogeneticist from the University of Leicester, said: "This is a big move forward for the development of new KMO inhibiting drugs. It is hoped that such compounds may ultimately be tested in clinical trials and prove beneficial for patients."

The findings from this research will now be used in the search for more effective treatments for Huntington's Disease.

Professor Sarah Tabrizi is the head of the Huntington's disease research team at University College London's Institute for Neurology.

Commenting on the research she says: "Unlocking the crystal structure of KMO is a real boost to our efforts to find treatments for this devastating disease. It provides a solid basis for the optimisation of inhibitor drugs like UPF 648 that are being developed by the global Huntington's disease research community. KMO is one of our top drug targets, and the [crystal structure](#) is a significant step along our roadmap to clinical trials of KMO inhibitors in patients."

Cath Stanley, Chief Executive of the Huntington's Disease Association also welcomed the findings: "This research is a really exciting piece of the jigsaw that enables us to understand a little more and takes us a step closer to being able to provide an [effective treatment](#) for Huntington's

Disease."

More information: "Structural basis of kynurenine 3-monooxygenase inhibition" *Nature*, 2013. [dx.doi.org/10.1038/nature12039](https://doi.org/10.1038/nature12039)

Provided by University of Manchester

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