

Drug Development for Huntington's Disease

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Abstract:

Huntington's disease is a rare but devastating inherited neurological disorder affecting around 8 people per 100,000. The typical onset of the disease is around the ages of 30-50 years old and the symptoms include chorea, a lack of coordination, cognitive dysfunction, and behavioural changes. Huntington's disease is caused by a mutation that causes an expansion of a polyglutamine repeat in the protein huntingtin. This leads to the formation of insoluble aggregates of the N terminal fragment of huntingtin that contains the polyglutamine repeat.

Elevated levels of the molecular chaperone heat shock protein 70 have been shown to reduce or dampen protein aggregation in polyglutamine diseases such as Huntington's disease. Over expression of heat shock protein 70 can be achieved via inhibition of heat shock protein 90. However the two classic heat shock protein 90 inhibitors Radicol and Geldanamycin have proven to be unable to cross the blood-brain barrier. Many heat shock protein 90 inhibitors have been investigated and reported as potential chemotherapeutic agents. Our project involves looking for a heat shock protein 90 inhibitor which can cross the blood-brain barrier and inhibit the formation of huntingtin aggregates. In this poster we report the initial work of this project, the synthesis of some known heat shock protein 90 inhibitors, which will next be tested for brain penetration and heat shock protein induction in vivo.