



TECHNOLOGY INFO SHEET



Use of kynurenic acid analogues for the treatment of Huntington's disease

Development status

► **Drug discovery**

Pre-clinical
Phase I.
Phase II.
Phase III.

IP status

In priority year
PCT I.
PCT II.

► **National/regional phase**

Validation

Challenge

Huntington's disease (HD) has an orphan indication with high medical need. Huntington's disease is a rare neurodegenerative disorder that progressively destroys mental capacity and motor control in patients. Given that no disease-modifying therapy for HD exists and that available symptomatic treatments are not highly efficacious, the medical need for this 'orphan' disease remains strong.

Technology

Huntington's disease (HD) is a progressive neurodegenerative disorder, the pathomechanism of which is not yet fully understood. Excitotoxicity is known to be involved in the development of HD, and antiglutamatergic agents may, therefore, have beneficial neuroprotective effects. One of these agents is the tryptophan metabolite kynurenic acid (KYNA), which is an endogenous NMDA receptor antagonist. However, its pharmacological properties rule out systemic administration in CNS disorders. We have tested a novel KYNA analogue in the N171-82Q transgenic mouse model for HD. The analogue exhibited several significant effects: it prolonged the survival of the transgenic mice, ameliorated their hypolocomotion, prevented the loss of weight and completely prevented the atrophy of the striatal neurons. As it induced no appreciable side-effect in this mouse model at the protective dose applied in a chronic dosing regimen, it would appear to call for further thorough investigations with a view to eventual clinical trials.

Keywords

Kynurenic acid analogue, Huntington's disease, NMDA receptor, excitotoxicity

Benefits

The therapeutic importance of kynurenic acid analogues is further increased by the fact that if the broad-spectrum receptor effects of KYNA are retained, they are capable of widespread anti-excitotoxic activity. KYNA can inhibit N-methyl-D-aspartic (NMDA) acid receptors at the strychnine-insensitive glycine binding sites. And it can also reduce the release of glutamate by inhibiting the presynaptic alpha-7-nicotinic acetylcholine receptors. Furthermore, a number of KYNA amides have shown selective inhibition of the NR2B subunit containing NMDA receptors, and NMDA receptors containing these subunits carry special importance in glutamate-induced excitotoxicity. Since glycine and polyamine site agents, NR2B subunit specific antagonists and ion channel blockers with lower affinity may come into consideration as NMDA receptor antagonists, as they exert acceptable side-effects, the KYNA amide analogues have a significantly improved side-effect profile compared to other ant glutamatergic agents. This offers a clear therapeutic advantage for patients.

Development status

On the basis of the promising preliminary results, the goal is to develop the preclinical dossier, complete investigations and launch phase 1 clinical trials. The exact mechanism of action is currently being investigated. Plans include further investigations of the compound in all the other models of neurodegenerative diseases.

IP status

The Hungarian patent was granted in 2016 (Patent no.: 230366).

What we are looking for

The University of Szeged is looking for partners to complete the preclinical trial and to further develop the technology.

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