Leprosy drug may be effective in Huntington's disease, study suggests

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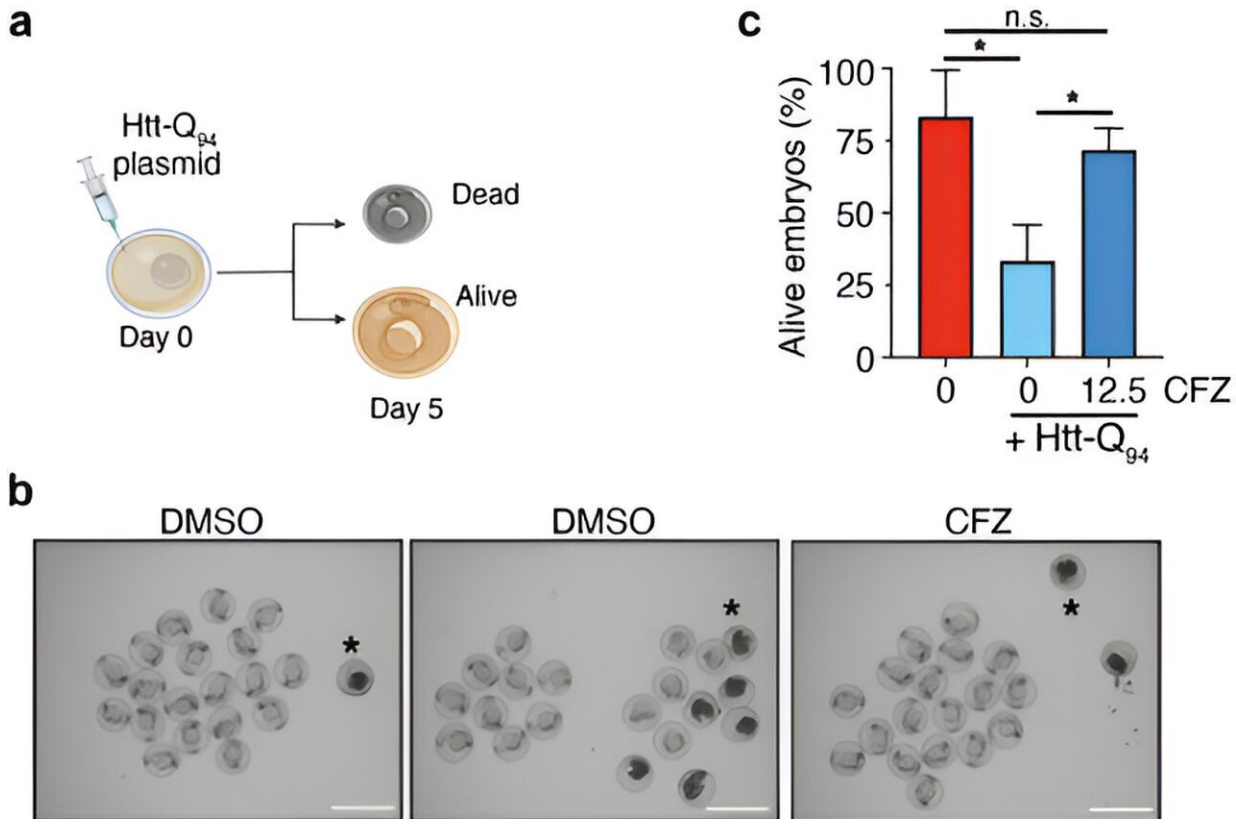

CFZ rescues polyQ toxicity in worms and developing zebrafish. (a) Scheme illustrating the pipeline followed to evaluate Htt-Q_{94} in developing zebrafish. (b) Representative images of zebrafish embryos 24 h after microinjection of the Htt-Q_{94}-CFP expressing plasmid or DMSO. Note the accumulation of dead embryos (black asterisk) upon Htt-Q_{94}-CFP expression, which was significantly rescued by CFZ (c) Quantification from the experiment defined in (a,b). (d) Scheme illustrating the pipeline used to evaluate the effect of CFZ in a worm model of polyQ toxicity. (e) Quantification of data from (d). Credit: *eBioMedicine* (2024).

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A preclinical study from Karolinska Institutet offers hope for treating severe neurodegenerative diseases with an existing drug. The study suggests that the leprosy drug clofazimine may be effective in the treatment of Huntington's disease.

The research group examined whether existing drugs could reduce the toxicity of so-called polyQ proteins. These proteins are found in patients with certain hereditary neurodegenerative diseases, including Huntington's disease, for which there is no cure.

Screening hundreds of drugs, they found that the leprosy drug clofazimine reduces the toxicity of polyQ proteins and restores mitochondrial function in zebrafish and worms. The finding supports the previous hypothesis that polyQ diseases are associated with the dysfunction of mitochondria, the organelles in charge of producing energy within cells.

The findings are published in the journal *eBioMedicine*.

"Our work not only suggests the interest of a specific drug for the treatment of polyQ neurodegenerative diseases, but also helps us to better understand what causes these diseases.

"It is possible to find new uses for old drugs, which reduces the time needed to find novel therapies," says last author Oscar Fernandez-Capetillo, Professor and research group leader at the Department of Medical Biochemistry and Biophysics at Karolinska Institutet.

A problem is that clofazimine is not very efficient in entering the

nervous system. The research group is now trying to figure out solutions to this limitation, by testing the efficacy of clofazimine in mammalian models of neurodegenerative disease.

"We hope that our discovery can be developed into a new medicine, but there are still some hurdles that need to be overcome," says Oscar Fernandez-Capetillo.

The researchers are also conducting similar drug screens in other age-related pathologies such as cancer and other neurodegenerative disorders.

More information: Xuexin Li et al, The anti-leprosy drug clofazimine reduces polyQ toxicity through activation of PPARγ, *eBioMedicine* (2024). DOI: 10.1016/j.ebiom.2024.105124

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