LS17-026 - Interrogating the fate of dopamine transporter mutants by pharmacochaperones

Abstract

By combining the power of chemical biology and neurogenetics this project aims at a step change in our understanding of pathophysiology of dopamine transporter mutations associated with human infantile dystonia/parkinsonism. Several point mutations in the human dopamine transporter hDAT impair protein folding in the endoplasmic reticulum and subsequent targeting to the synaptic compartment. We recently provided a proof-of-principle that small chemical compounds support protein folding of mutant hDAT in the genetic model Drosophila resulting in a functional recovery. The main challenges are to identify additional compounds and to gain mechanistic insights into how specific chemical features influence protein conformation and spatio-temporal distribution of individual hDAT mutants within the dopaminergic brain circuit. We will take advantage of the well-mapped chemical space of hDAT ligands to screen for compounds in complementary assays for chaperoning activities towards hDAT mutants, i.e. in cell culture and in a Drosophila paradigm for DAT-dependent sleep regulation. We propose to capitalize on the pharmacochaperones as tools to interrogate cutting-edge transgenic Drosophila strains to study the fate of individual hDAT mutants and their impact on ER stress, neuronal survival and synaptic connectivity. With an evolutionary conserved dopaminergic system, we propose to translate our mechanistic insights to human protein folding diseases via patient-derived iPS cell lines.

Scientific disciplines:
Chemical Biology (40%) | Pharmacodynamics (30%) | Neurobiology (30%)

Keywords:
dopamine transporter,

Principal Investigator:	Michael Freissmuth
Institution:	Medical University of Vienna
Co-Principal Investigator(s):	Thomas Hummel (University of Vienna)

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Further links to the persons involved and to the project can be found under
https://www.wwtf.at/funding/programmes/ls/LS17-026/