# Exploring and enhancing Karyopherin beta-2 disaggregate activity

https://neurodegenerationresearch.eu/survey/exploring-and-enhancing-karyopherin-beta-2-disaggregate-activity/

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USA

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**Research Abstract**

Project summary There are no effective treatments for various fatal neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), or multisystem proteinopathy (MSP) in which specific RNA-binding proteins (RBPs) with prion-like domains mislocalize and aggregate in the cytoplasm of degenerating neurons. For example, wild-type FUS, TAF15, and EWSR1 accumulate in cytoplasmic aggregates and are

depleted from the nucleus in degenerating neurons in some forms of FTLD, whereas wild- type or mutant hnRNPA1 and hnRNPA2 exhibit this phenotype in degenerating neurons and other tissues in MSP. For all of these RBPs, which bear a PY-nuclear localization signal (NLS), as well as TDP-43, which bears a distinct canonical NLS, a key pathological event is their mislocalization to cytoplasmic aggregates. Indeed, from this perspective ALS, FTD, and MSP can be viewed fundamentally as nuclear-transport disorders. We hypothesize that agents able to reverse RBP mislocalization and aggregation and thereby restore the RBPs to native form, function, and nuclear localization would mitigate toxicity by simultaneously eliminating: (1) any toxic gain of function of the misfolded form; and (2) any loss of function due to sequestration in cytoplasmic aggregates. Remarkably, our preliminary findings suggest that the nuclear import factor, Karyopherin-?2 (Kap?2, also known as transportin), is such an agent. Thus, Kap?2 can prevent and reverse the aggregation of various RBPs bearing a PY-NLS, and subsequently transport them back to the nucleus. A role for Kap?2 as a nuclear import factor is well established. However, our discovery that Kap?2 has disaggregase activity is unprecedented. Mutations in the PY-NLS of FUS are linked with ALS, and these mutations directly weaken the interaction between Kap?2 and FUS. Here, we propose a series of multidisciplinary studies that employ pure protein biochemistry, yeast, mammalian neuronal culture, and Drosophila models of RBP-opathies to meet two aims: (1) Define Kap?2 activity in preventing and reversing aggregation, mislocalization, and toxicity of specific disease-linked RBPs in vitro and in vivo; (2) Engineer enhanced Kap?2 variants to recognize and disaggregate ALS-linked FUS variants bearing mutations in their PY-NLS. Thus, we will exploit Kap?2 as a bifunctional disaggregase and nuclear import factor to combat pathogenesis associated with cytoplasmic mislocalization and aggregation of FUS, TAF15, EWSR1, hnRNPA1, and hnRNPA2. Our proposed studies will elucidate how a nuclear import factor, Kap?2, can be harnessed and engineered to prevent and reverse these deleterious RBP mislocalization and misfolding events, which will empower the development of therapies for specific forms of ALS, FTD, and MSP.

**Further information available at:**

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