Weill Cornell Medicine

Iron Chelators for the Treatment of Adult Neuronal Ceroid Lipofuscinosis

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Background & Unmet Need

- Point mutations in cysteine string protein-α (CSPα) cause dominantly inherited adult-onset neuronal ceroid lipofuscinosis (ANCL), a rapidly progressing and lethal neurodegenerative disease
- There are currently no disease-specific treatments approved for ANCL
- ANCL mutations are proposed to trigger CSPα aggregation, but the mechanism of oligomer formation remains unclear
- **Unmet Need:** Novel therapeutic approaches that target CSPα to prevent disease progression

Technology Overview

- **The Technology:** Use of iron chelators to disrupt CSPα aggregation for the treatment of ANCL
- **The Discovery:** The normally palmitoylated cysteine string region of CSPα loses palmitoylation in ANCL mutants, enabling oligomerization via ectopic binding of iron-sulfur (Fe-S) clusters
- Pharmacological iron chelation with deferiprone (L1) and deferoxamine (Dfx) mitigates the oligomerization of mutant CSPα
- Iron chelation also led to partial rescue of downstream SNARE defects and the pathological hallmark of lipofuscin accumulation

Inventors:
Manu Sharma
Nima N. Naseri

Patents:
US Application Filed

Publications:
Naseri et al. *Nat Struct Mol Biol*. 2020.

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Technology Applications

- Treatment of ANCL symptoms and prevention of disease progression

Technology Advantages

- The iron chelators L1 and Dfx are already approved for the treatment of iron overload, potentially leading to an accelerated development timeline
- L1 efficiently crosses the blood-brain barrier and is orally available
- Potential to be a disease-modifying therapy that slows disease progression, rather than simply treating symptoms

Supporting Data / Figures

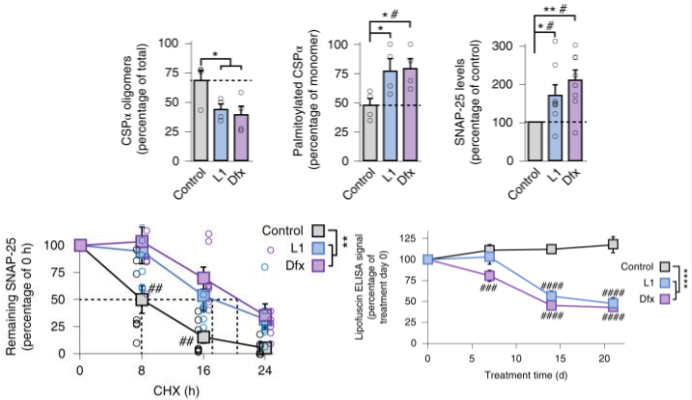

Figure 1: In ANCL patient-derived induced neurons, iron chelators alleviate CSPα oligomerization, the SNAP-25 chaperoning defect and lipofuscin accumulation

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