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Orally Administered PROTAC® Molecules Selectively Clear Pathologic Proteins in CNS & Muscle

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Abstract #8843

Objective: PROteolysis Targeting Chimeras (PROTAC®) are heterobifunctional small molecules that bind to both an E3-ubiquitin ligase and a target protein leading to ubiquitination and subsequent proteasomal degradation of pathologic proteins.

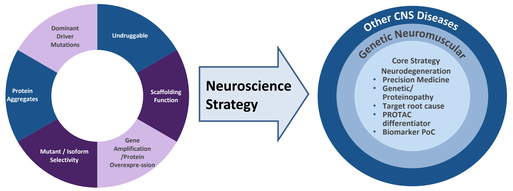
Our platform has enabled the discovery of PROTAC® degrader molecules, that when orally administered, cross the blood-brain barrier to degrade proteins with toxic gain-of-function in neurodegeneration (as we have previously shown for tau) and neuromuscular diseases.

Highlighted Here:

- **Huntington's Disease:** Novel heterobifunctional PROTAC® degrader molecules that target soluble mutant Huntingtin protein (mHTT) for degradation and spare wild-type HTT (WT-HTT).
- **Neuromuscular Disease:** Degradation of disease-causing proteins by orally administered PROTAC® molecules clear pathology and improve endurance and function in a severe mouse model.
- **Neurodegenerative Disease:** We show for the first time, following oral administration that PROTAC molecules degrade across species, with specificity, and broadly biodistribute across the primate brain to reduce target proteins in deep brain structures anatomically involved in disease progression.

PROTAC® molecules harness the ubiquitin-proteasome system to degrade proteins

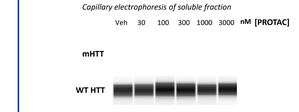
PROTAC® molecules differentiate from inhibitors



Huntington's Disease: Ligand chemistry enables allele-selective PROTAC® degradation of mHTT

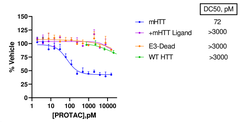
PROTAC degradation of soluble mHTT

Capillary electrophoresis of soluble fraction



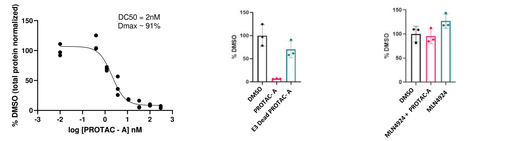
PROTAC spares wild-type HTT

PROTAC-induced degradation of mHTT, spares WT HTT, and is on mechanism



Neuromuscular Target: PROTAC® degraders remove toxic aggregating protein within myotubes

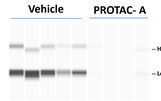
PROTAC-A degrades toxic aggregating protein in iPSC- myotubes from patients via E3/proteosome- dependent mechanism.



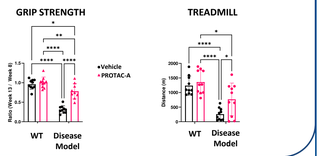
*MLN4924 is a neddylation inhibitor

Oral PROTAC® administration removes toxic protein within muscle and improves muscle function

Neuromuscular degeneration Mouse Model (3xQD PO)



Neuromuscular degeneration Mouse Model (PROTAC-A chronic oral administration) improves function and endurance

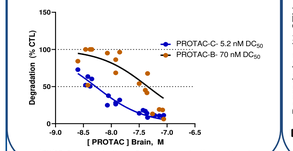


PROTAC degrades toxic protein aggregates in a highly aggressive murine disease model with improved function (grip strength), endurance (treadmill), and lifespan (not shown).

PROTAC® -B degrades scaffolding target in iPSC-derived microglia and is on mechanism

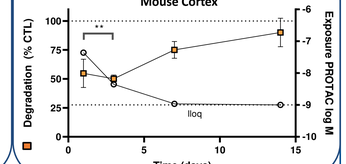
Single oral PROTAC® administration rapidly degrades target in brain (concentration-dependent and durable)

PROTAC-optimization -Dose-Response PK/PD* In Mouse Cortex 24h post single oral dose



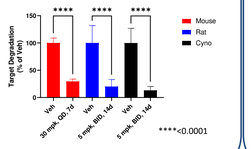
*PK/PD- Pharmacokinetic and Pharmacodynamic effect relationship

Single oral dose PROTAC PK/PD* Time-Course – Mouse Cortex

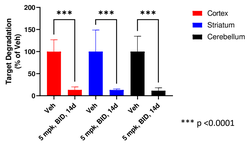


Oral PROTAC® induced degradation with biodistribution to deep anatomic brain regions in Primates

Target degradation in brain across species (mouse, rat, cyno) after oral PROTAC dosing



Robust biodistribution in cynomolgus monkey brain after oral dosing (cortex, cerebellum, & striatum)

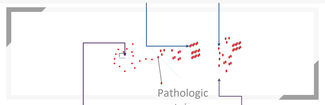


PROTAC® degraders: a differentiated opportunity vs. other modalities used for CNS diseases

PROTAC® degrader small molecules can overcome the limitations of other platforms

PROTAC *Potential vs. Other Modalities*

- Reduce intra- and extracellular pathologic protein
- Discriminate between wild type and pathologic protein
- Oral administration with BBB biodistribution



ASO	Ab
• Requires intrathecal dosing • Does not discriminate wt from pathologic protein	• Blocks only extracellular pathologic protein • IV dosing results in only 0.5% in CSF

Oral PROTAC® degrader molecule is highly selective in brain

PROTAC is a highly selective degrader molecule

Volcano plot (log2 FC vx. –log10 p-value)

- 24-hour PROTAC vs vehicle control
- Target is most significantly changed protein in cortex
- $p > 10^{-17}$

TMT Proteomic analysis in brain 24 h following oral administration

Conclusions

PROTAC® molecules differentiate from conventional inhibitor molecules and genomic modalities and represent a therapeutic new horizon in CNS diseases.

Our PROTAC® molecules:

- Degrade intracellular pathologic mHTT and spare WT HTT.
- Degrade pathologic proteins in muscle in severe neuromuscular disease model to improve function and endurance.
- Degrade target proteins in neurons, muscle cells, and microglia in preclinical models, including those derived from human iPSCs.
- Can be optimized for oral absorption, high selectivity, biodistribution, and pharmacodynamic effect across species.
- Biodistribute, following oral administration, across the primate brain to deep neuroanatomic structures that are relevant for the treatment of Huntington's Disease and other CNS diseases.

References

PROTAC review: Békés, M., Langley, D.R. & Crews, C.M. PROTAC targeted protein degraders: the past is prologue. Nat Rev Drug Discov 21, 181–200 (2022).

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