DRP1 PROGRAM
NON-CONFIDENTIAL SUMMARY

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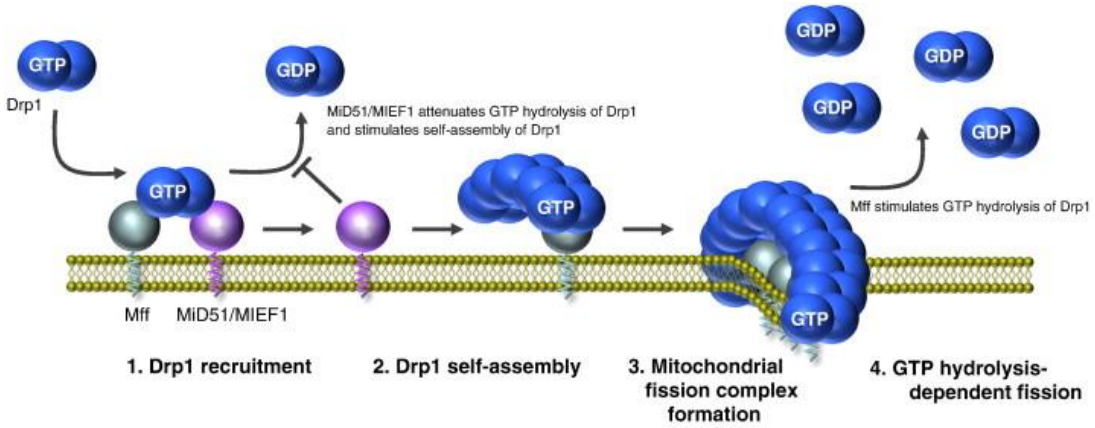
DRP1 INHIBITOR - CONCEPT

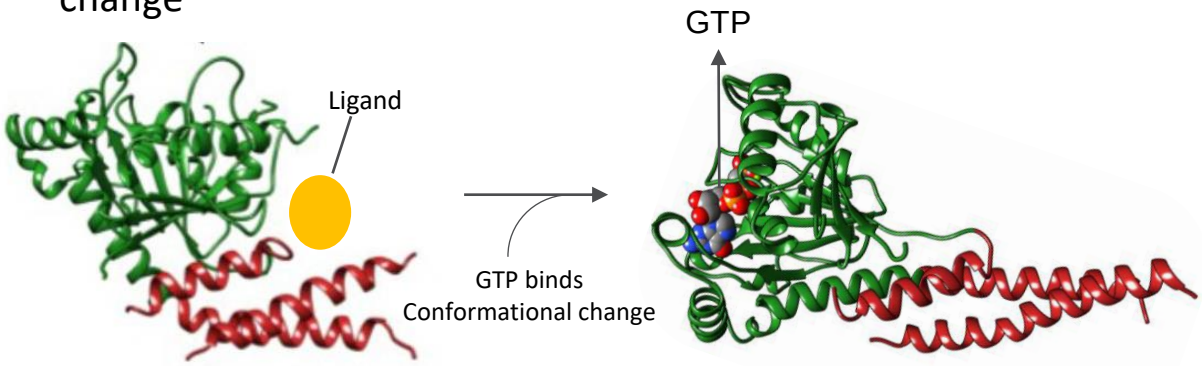
- Drp1 is essential for mitochondrial fission
- A member of the Dynamin superfamily, a GTPase linked mechano-enzymes that oligomerizes and constricts mitochondria
- Recruited to mitochondria by membrane receptors Mff, MiD49/51, and Fis1



Target Indications

- Huntington
- Alzheimer
- Parkinson
- Charcot-Marie-Tooth 2B

Strategy: Target a pocket in the assembly that stabilizes the closed conformation and thereby prevents conformation change

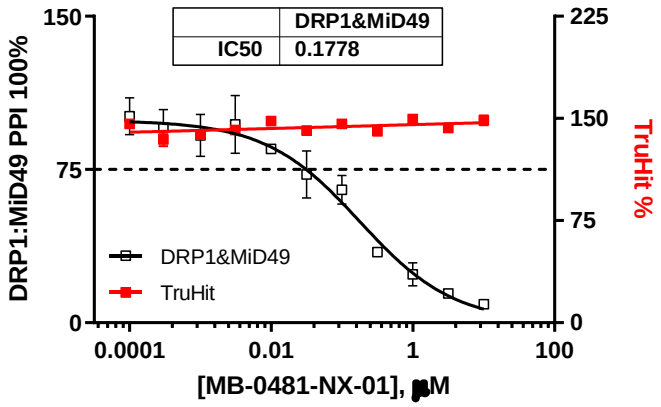


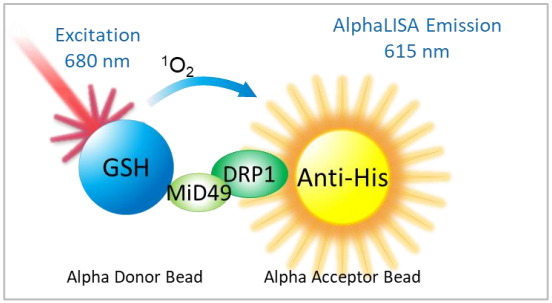
Disambiguation: DRP1; Dynamin-Related Protein 1 = DNM1L gene

DRP1 INHIBITOR (MB-0481) - IN VITRO EXAMPLE

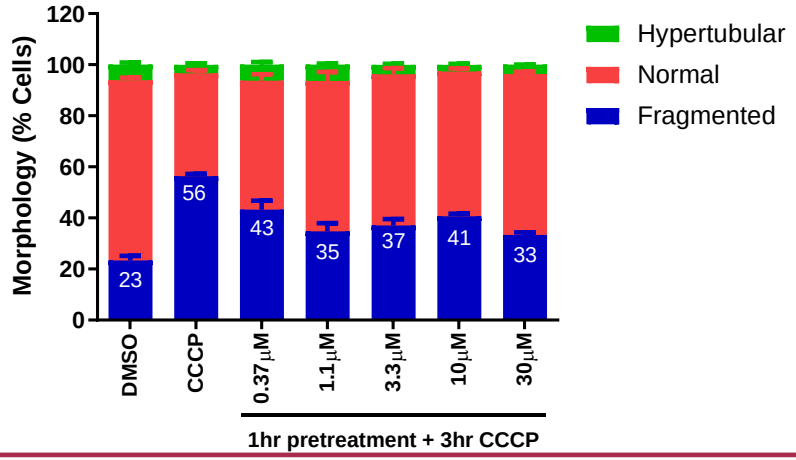
MB-0481

DRP1:MiD49 AlphaLISA

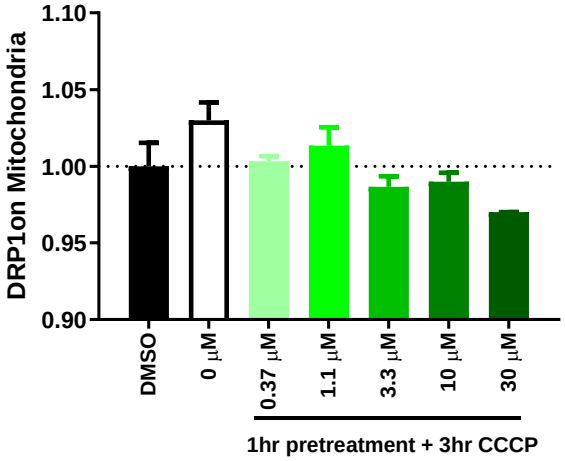




Mitochondrial Morphology



DRP1 Recruitment



DRP1 INHIBITOR - SUMMARY

Identified a novel series of DRP1 inhibitors which exhibit good on-target biochemical and cellular potency

- Patent filed
- In vitro: Assays established (IC50 0.2 uM PPI assay)
- In vivo: Good Safety profile, up to 300 mg/kg, attractive overall ADME profile
- Molecule: Unique binding mode
- Publication (2023): Furuya T, Lin J, Afanaseva A, Molz L, Lagu B, Ma B. Discovery of Potent Allosteric DRP1 Inhibitors by Disrupting Protein-Protein Interaction with MiD49. ACS Med Chem Lett. 2023 Jul 24;14(8):1095-1099. doi: 10.1021/acsmedchemlett.3c00223. PMID: 37583827; PMCID: PMC10424310.

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