**Docket #:** S22-050

# Potent and selective small molecule inhibitor of Drp1 mediated pathological mitochondrial fission for the treatment of mitochondrial dysfunction-associated diseases

Mitochondrial fragmentation and dysfunction is a key contributor to multiple clinical pathologies, including neurodegenerative disorders, sepsis, and myocardial infarction. The accumulation of fragmented mitochondria in otherwise healthy tissue results in a heightened inflammatory state that contributes to disease pathology, reduces cellular ATP levels, increases reactive oxygen species and triggers cell death. Drp1 mediates both physiological mitochondrial fission, a process essential for maintaining mitochondrial quality and functioning. as well as pathological (excessive) fission. Therefore, Drp1 has proven difficult to drug on account of its important role in maintaining normal mitochondrial physiology.

Inventors from Stanford's Mochly-Rosen lab have identified a small molecule that targets a druggable site on the Drp1 protein, specifically blocking a its interaction with a partner protein that mediates its pathological responses- retaining normal function of Drp1 while blocking its pathological activity.

The small molecule replicates the previously characterized activity of peptide P110, but without the inherent limitations of a peptide drug. P110 is not orally bioavailable, has a limited penetration to the brain and has a short halflife in vivo, thus limiting its translational potential. The small molecule mimicking the activity of P110 is expected to overcome these pharmacokinetic barriers.

In a mouse model of sepsis, the small molecule increased survival in animals challenged with LPS with nanomolar potency, while also improving symptom scores.

## Applications

- Small molecule therapeutic for the treatment of:
- Neurodegeneration
- Sepsis
- Myocardial infarction

## Advantages

- New chemical entity and associated chemical space
- Improved pharmacokinetics over existing Drp1 inhibitor, invented by the same laboratory
- Improved selectivity to pathological Drp1 functions only
- Binding mechanism retains baseline activity levels of Drp1

## Patents

- Published Application: WO2023150639

## Innovators

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