Small Molecule Inhibitors of SARM1 Prevent Axonal Degeneration in vitro and in vivo

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Axonal degeneration is an early and ongoing event that causes disability and disease progression in many neurodegenerative disorders of the central, peripheral, and ocular nervous systems, including multiple sclerosis, ALS, peripheral neuropathies, and glaucoma. SARM1 is the central driver of an evolutionarily conserved program of axonal degeneration downstream of inflammatory, mechanical, metabolic, or chemical insults to the axon. SARM1 contains an intrinsic NADase enzymatic activity essential for its pro-degenerative functions, making it a compelling therapeutic target to treat neurodegeneration characterized by axonopathy.

Disarm has developed a high-content screening platform and identified proprietary drug-like small molecule inhibitors of SARM1. These inhibitors protect rodent and human axons in vitro from mechanical, chemotherapeutic and mitochondrial damage. In sciatic nerve transection, SARM1 inhibitors prevent increases in plasma NfL, a clinically accessible biomarker of axonal degeneration. In a paclitaxel model of chemotherapy-induced peripheral neuropathy (CIPN), SARM1 inhibitors protect axonal structure (plasma NfL) and function (SNAP amplitude). This is the first demonstration that pharmacological inhibition of SARM1 can reproduce the axonal protective phenotype observed in SARM1 knockout mice. The availability of SARM1-dependent biomarkers of axonal degeneration enables rapid translation of SARM1 inhibitors from discovery to the clinic. SARM1 inhibitors have the potential to prevent axonal degeneration in peripheral and central axonopathies and provide a translational disease-modifying treatment for these disorders.

1. SARM1 Drives Rapid NAD+ Loss Leading to a Bioenergetic Crisis and Axonal Degeneration

2. SARM1 - The Central Driver of Axonal Degeneration in Neurological Diseases

3. A Proprietary Screening Platform Identified Small Molecule SARM1 Inhibitors

4. SARM1 Inhibitors Protect from Mechanical, Chemical and Mitochondrial Insults

5. SARM1 Inhibitors Protect Human Axons

6. SARM1 Inhibitor Protects Axons in vivo After Sciatic Nerve Transection

7. SARM1 Inhibitors Prevent Neuropathy in vivo in a Paclitaxel CIPN Model

Conclusions
- Disarm has advanced a proprietary R&D platform to discover small molecule inhibitors of SARM1, the central driver of axonal degeneration.
- We are providing the first demonstration that Disarm’s novel small molecule SARM1 inhibitors reproduce the axonal protection phenotype seen in SARM1 knockout. Disarm’s compounds:
  - Protect axons in vitro from multiple pathological insults
  - Protect human iPSC-derived motor axons from traumatic injury
  - Prevent axonal degeneration and preserve axonal function in vivo in a rodent model of chemotherapy-induced peripheral neuropathy (CIPN)

Disarm is developing small-molecule SARM1 inhibitors for patients with neurological diseases such as MS, ALS and CIPN.