SARM1 Deletion Prevents Degeneration of Peripheral and Central Axons
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Axonal degeneration causes disability and disease progression in chronic and acute diseases of the central, ocular, and peripheral nervous systems such as multiple sclerosis, amyotrophic lateral sclerosis, glaucoma, and peripheral neuropathies. Although substantial evidence indicates that these neurological diseases are primarily the result of damage to axons, there are currently no therapies to prevent axonal degeneration.

SARM1 has been identified as the central mediator of a cell-autonomous program of axonal degeneration and loss of axonal function. A variety of genetic, immune, metabolic insults, and injuries activate SARM1 enzymatic function, which directly leads to axonal degeneration. SARM1 is therefore an attractive target for development of a novel class of potentially disease-modifying therapeutics for central, ocular, and peripheral neurological diseases characterized by axonopathy.

Disarm is developing small-molecule inhibitors of SARM1 to reproduce the axonal protective phenotype seen with SARM1 genetic deletion. We have established SARM1-dependent peripheral and central axonal disease models to assess in vivo PK/PD of therapeutic candidates. We discovered that cADPR is a proximal biomarker of SARM1 activity in vitro and in vivo. We also established that neurofilament light chain (NF-L), an axon-specific cytoskeletal protein released when axons degenerate, is a CSF and blood biomarker of SARM1-dependent CNS and PNS axonal degeneration. Blood NF-L is increasingly being used as a clinical biomarker of central and peripheral neurodegeneration to measure disease progression and disease-modifying therapy effectiveness. Disarm is developing two small-molecule inhibitors in parallel, one for central axonopathies, including multiple sclerosis, and one for peripheral axonopathies such as chemotherapy-induced peripheral neuropathy.

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. SARM1 Loss of Function Protects in Axotomy and Chemical Injury Models in vitro

4. cADPR is a Proximal Biomarker of SARM1 Activation after Axonal Injury in vitro

5. NF-L is a Biomarker of Axonal Degeneration in vitro

6. cADPR and NF-L Increase after Peripheral and Central Nerve Injury in vivo

7. SARM1 Genetic Deletion Prevents Increase of cADPR and Plasma NF-L in Sciatic Nerve Transection Model

8. SARM1 Genetic Deletion Prevents Increase of cADPR and Plasma NF-L in CIPN Model

9. SARM1 Genetic Deletion Prevents Increase of cADPR and Plasma NF-L in Optic Nerve Crush Model

Conclusions
- SARM1 genetic deletion protects axons from traumatic and chemical nerve damage in vitro and in vivo
- cADPR is a proximal biomarker of SARM1 enzymatic activity in vitro and in vivo
- NF-L, a prognostic biomarker of neurodegeneration increasingly used in the clinic, is released in blood following CNS, ocular, and PNS axonal degeneration in a SARM1-dependent manner
- Disarm is developing small-molecule SARM1 inhibitors as potentially disease-modifying therapeutics for patients with central and peripheral nervous system diseases such as multiple sclerosis and CIPN