# SARM1 Signaling In the Injured Nervous System

## May 9

### Tuesday, 12:30 pm

### Zoom Only

***SPEAKER:***


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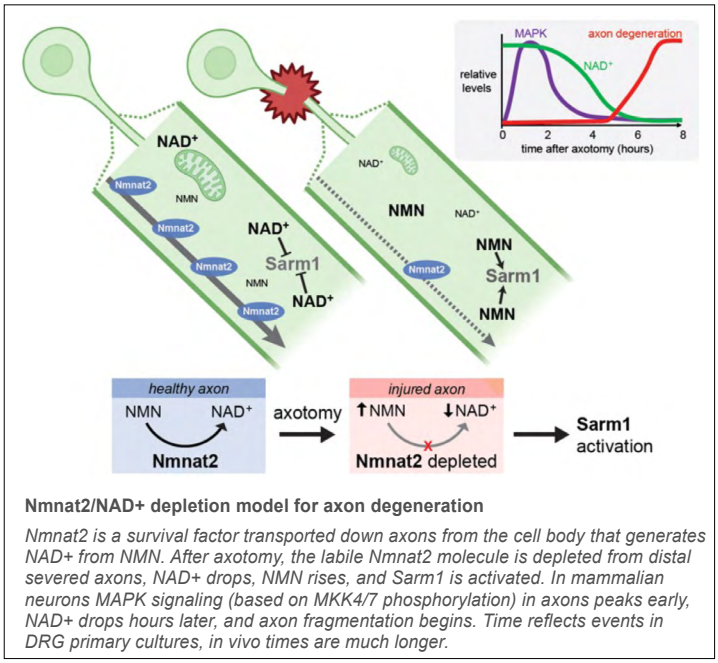
## Abstract


Axon degeneration is a prominent feature of the injured nervous system, occurs across neurological diseases, and drives functional loss in neural circuits. We discovered that injured axons are capable of actively driving their own destruction through the sterile-alpha and TIR motif containing 1 (SARM1) protein. Early studies of Wallerian degeneration highlighted a central role for NAD+ metabolites in axon survival, and this association has grown even stronger in recent years with a deeper understanding of SARM1 biology. This seminar will discuss our current knowledge of SARM1 function in vivo, and our evolving understanding of its complex architecture and potential regulation by injury-dependent changes in the local metabolic environment. The field is converging on a model whereby SARM1 acts as a sensor for metabolic changes that occur after injury, and then drives catastrophic NAD+ loss to promote degeneration. However, a number of observations suggest that SARM1 biology is much more complicated, and there remains much to learn about how SARM1 governs nervous system responses to injury or disease.


**Nmnat2/NAD+ depletion model for axon degeneration**

*Nmnat2 is a survival factor transported down axons from the cell body that generates NAD+ from NMN. After axotomy, the labile Nmnat2 molecule is depleted from distal severed axons, NAD+ drops, NMN rises, and Sarm1 is activated. In mammalian neurons MAPK signaling (based on MKK4/7 phosphorylation) in axons peaks early, NAD+ drops hours later, and axon fragmentation begins. Time reflects events in DRG primary cultures, in vivo times are much longer.*

### *Publications:*


1. Sambashivan S, Freeman MR. *SARM1 signaling mechanisms in the injured nervous system.* Curr Opin Neurobiol. 2021 Aug;69:247-255. doi: 10.1016/j.conb.2021.05.004. Epub 2021 Jun 25. PMID: 34175654; PMCID: PMC8387414.

2. Hsu JM, Kang Y, Corty MM, Mathieson D, Peters OM, Freeman MR. *Injury-Induced Inhibition of Bystander Neurons Requires dSarm and Signaling from Glia.* Neuron. 2021 Feb 3;109(3):473-487.e5. doi: 10.1016/j.neuron.2020.11.012. Epub 2020 Dec 8. PMID: 33296670; PMCID: PMC7864878.

3. Neukomm LJ, Burdett TC, Seeds AM, Hampel S, Coutinho-Budd JC, Farley JE, Wong J, Karadeniz YB, Osterloh JM, Sheehan AE, Freeman MR. *Axon Death Pathways Converge on Axundead to Promote Functional and Structural Axon Disassembly. Neuron.* 2017 Jul 5;95(1):78-91.e5. doi: 10.1016/j.neuron.2017.06.031. PMID: 28683272.