

The SARM1 Axon Degeneration Pathway: Mechanistic Insights and Therapeutic Opportunities

September 11

Thursday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:



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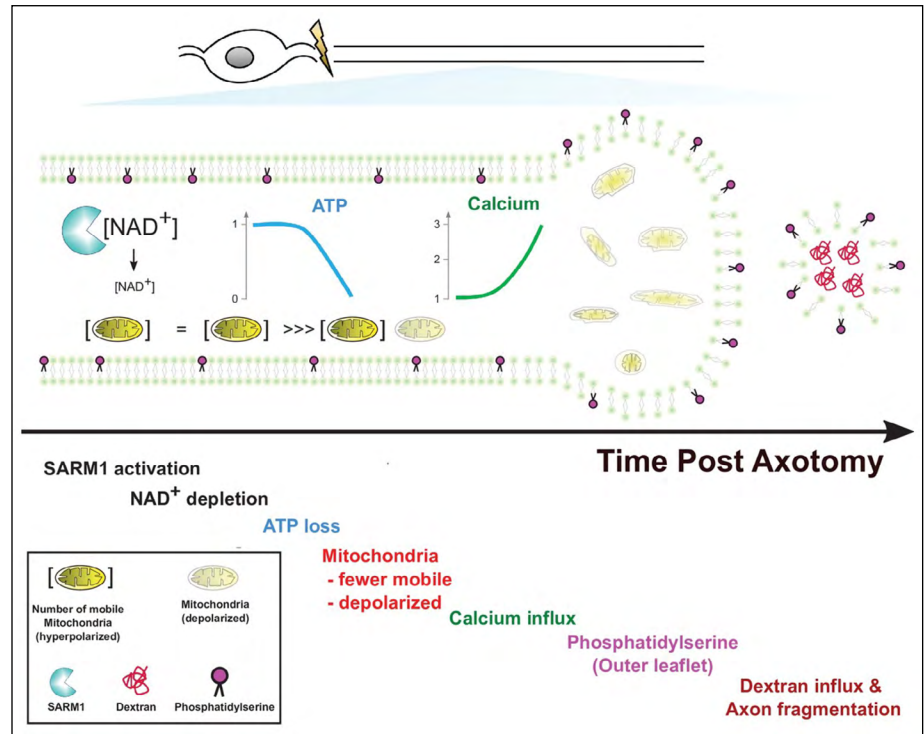
Host: Vibhu Sahni, Ph.D.

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Abstract



Axon loss drives morbidity and progression of many common neurological diseases including peripheral neuropathy, glaucoma, traumatic brain injury, multiple sclerosis, and neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, and ALS. Axon degeneration is a genetically encoded program of subcellular self-destruction. We use *Drosophila*, mice, and human iPSC-derived neurons to define the molecular mechanisms of the axon degeneration pathway. We identified SARM1 as the central executioner of the axonal degeneration program and demonstrated that it is the founding member of an ancient class of enzymes that cleave the essential metabolite NAD. Using these mechanistic insights, we have developed small molecule inhibitors to block the SARM1 pathway that are currently in clinical trials as potential therapies for neurodegenerative disease.

Publications

1. Figley M.D., Gu W., Nanson J.D., Shi Y., Sasaki Y., Cunnea K., Malde A.K., Jia X., Luo Z., Saikot F.K., Mosaib T., Masic V., Holt S., Hartley-Tassell L., McGuinness H.Y., Manik M.K., Bosanac T., Landsberg M.J., Kerry P.S., Mobli M., Hughes R.O., Milbrandt J., Kobe B., DiAntonio A., Ve T. (2021) *SARM1 is a metabolic sensor activated by an increased NMN/NAD⁺ ratio to trigger axon degeneration*. *Neuron* 109: 1118-1136.
2. Krus, K.L., Strickland, A., Yamada, Y., Devault, L., Schmidt, R.E., Bloom, A.J., Milbrandt, J., and DiAntonio, A. (2022) *Loss of Stathmin-2, a hallmark of TDP-43-associated ALS, causes motor neuropathy*. *Cell Reports*, 111001.
3. Sato-Yamada, Y., Strickland, A., Sasaki, Y., Bloom, A.J., DiAntonio, A., and Milbrandt, J. (2022) *A SARM1-mitochondrial feedback loop drives neuropathogenesis in a Charcot-Marie-Tooth disease type 2A rat model*. *J.C.I.* 132: e161566.