Washington University in St. Louis
Office of Technology Management

A COMPANION DIAGNOSTIC TO SARM1 INHIBITORS FOR NEURODEGENERATIVE DISEASES

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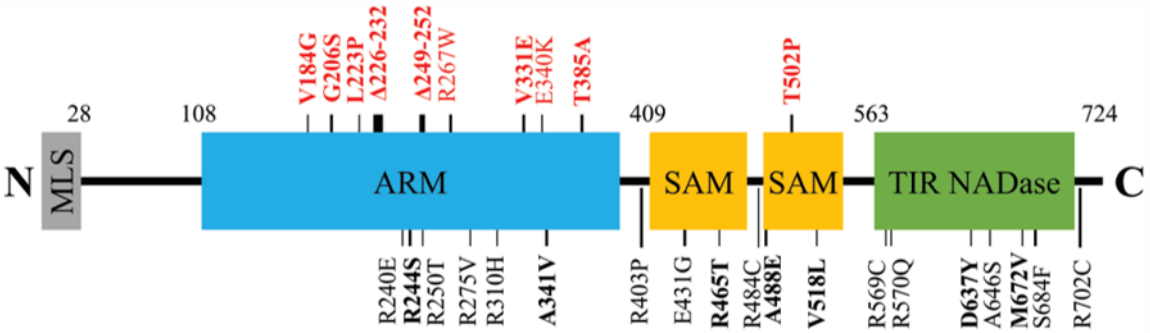
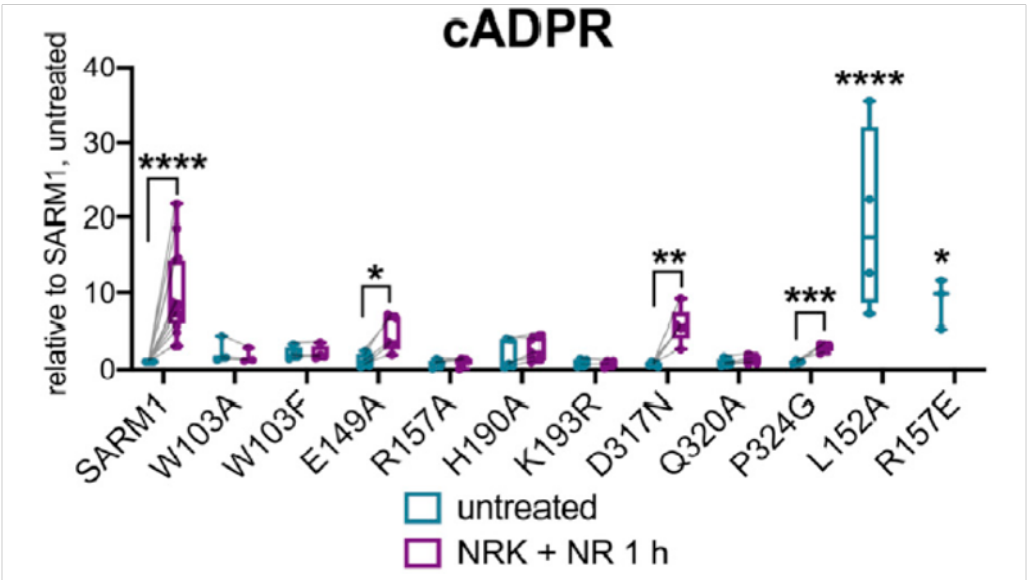
Technology Description

Researchers at Washington University, led by Jeffrey Milbrandt, have developed a companion diagnostic for SARM1 inhibitors that detects pathogenic variants of the SARM1 gene. Patients with one of several identified variants of SARM1 would respond well to SARM1 inhibitor therapy for treatment of neurodegenerative diseases like ALS.

The inventors have discovered that a group of SARM1 variants confer an increased risk of neurodegenerative disease, including ALS. Many of these variants create a hyperactive or constitutively-active SARM1 that promotes axon degradation and could be susceptible to inhibitors. The SARM1 activity level is measured by expressing the variants in primary neurons and measuring the level of cADPR, a product of SARM1 cleavage of NAD+.





(Top) Schematic of SARM1 variants found in ALS patients. Variants in red produce constitutively-active SARM1, and bolded variants were found in multiple patients. (Bottom) The effect of variants on SARM1 activity is assayed by measuring cADPR levels in primary neurons after NR treatment.

Stage of Research

The inventors have identified variants of SARM1 from patients with neurodegenerative diseases, including ALS. They verified the effect of each variant on neurodegeneration by lentiviral infection both *in vitro* and in a mouse model.

Publications

- Figley MD, Gu W, Nanson JD, Shi Y, … Ve T. (2021). SARM1 is a metabolic sensor activated by an increased NMN/NAD+ ratio to trigger axon degeneration. *Neuron*, 109:1118-1136.
- Bloom AJ, Mao X, Strickland A, Sasaki Y, Milbrandt J, & DiAntonio A. (2021). Constitutively active *SARM1* variants found in ALS patients induce neuropathy. *bioRxiv*, 439886.

Applications

- Companion diagnostic for SARM1 inhibitor therapy of neurodegenerative disease

Key Advantages

- Identifies patients susceptible to SARM1 inhibitors

Patents: Pending

Related Web Links: Milbrandt Profile & Lab; DiAntonio Profile & Lab; Mao Profile; Bloom Profile