北京大学
PEKING UNIVERSITY

SARM1八聚体结构功能分析

Analysis on the structure and function of SARM1 octamer

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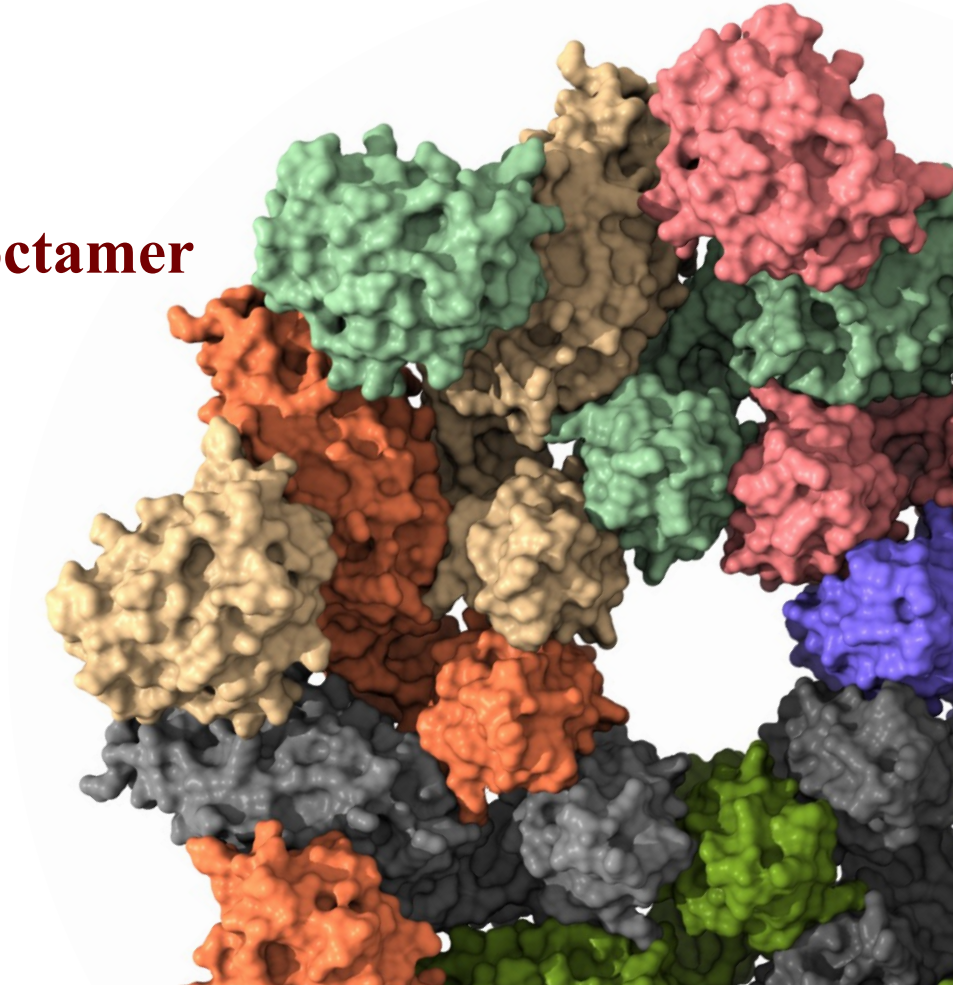
组员： 谭栩 刁天 张明钰



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Axon Degeneration

Stroke

Parkinson' s disease

Amyotrophic lateral sclerosis

Multiple sclerosis

Traumatic brain injury

Spinal muscular atrophy

↓

Injured axons

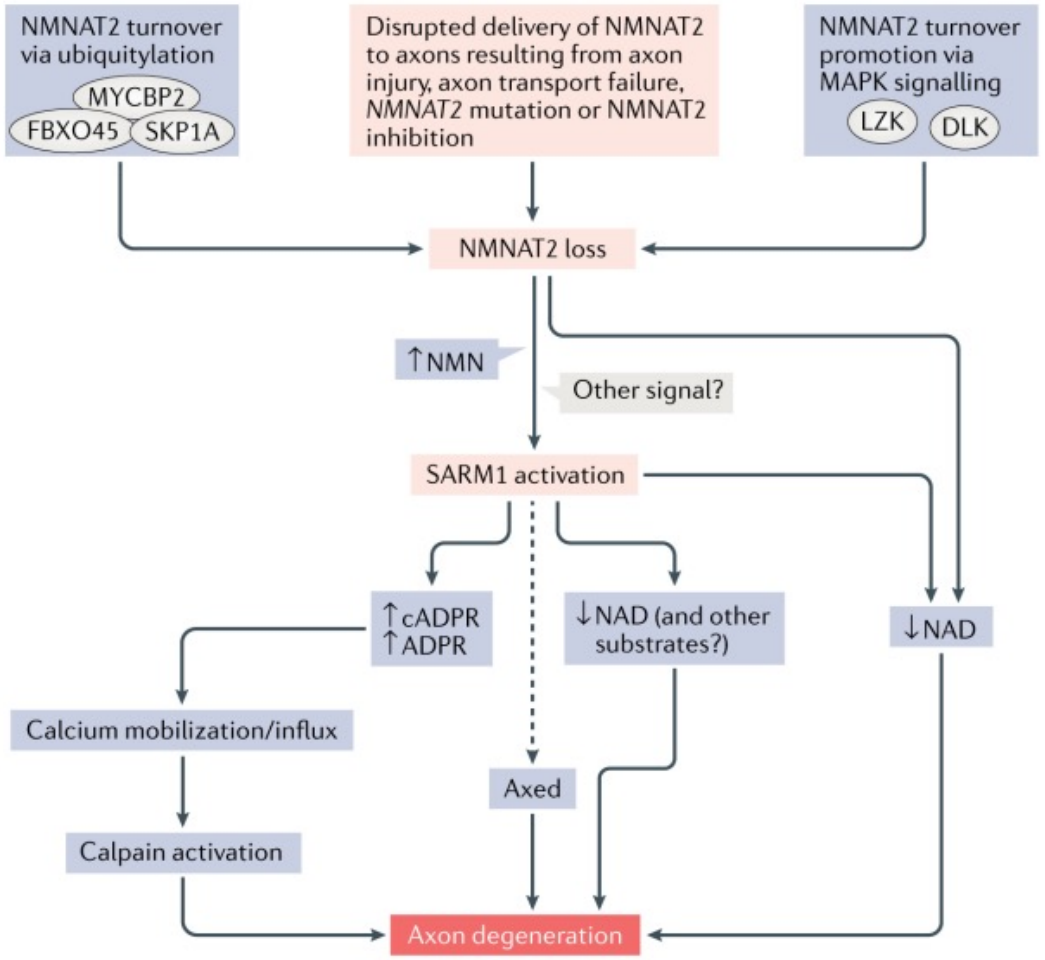
swelling

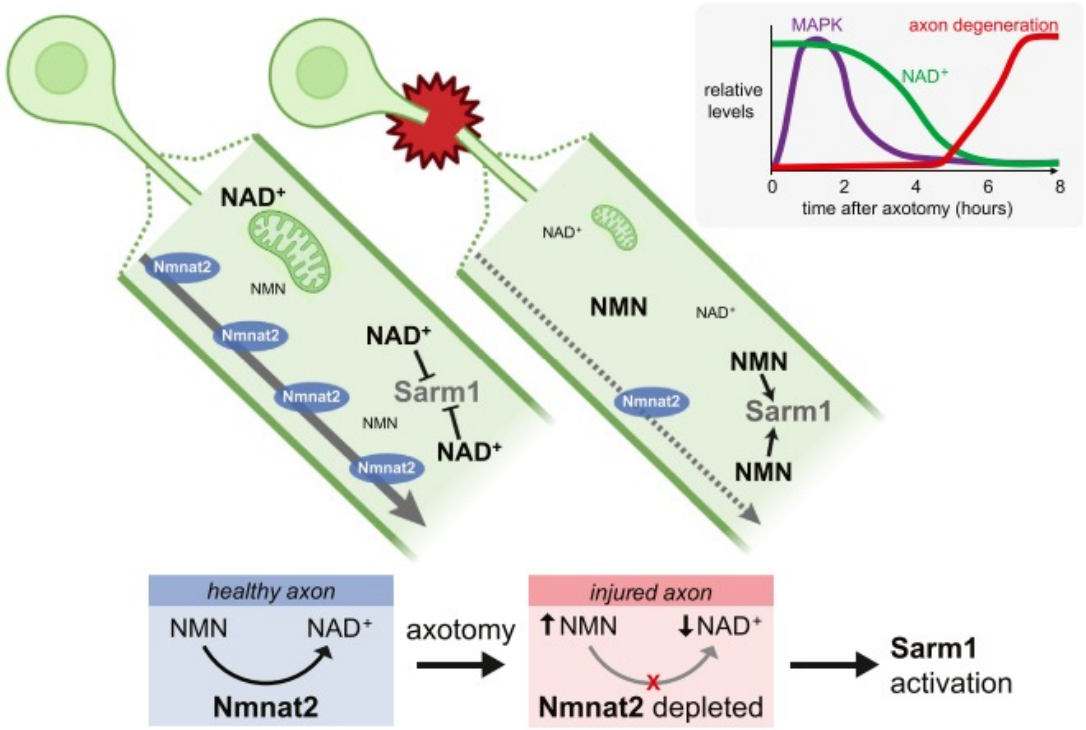
beading ↓

fragmentation

Wallerian Degeneration

Nmnat2/NAD+ depletion model for axon degeneration





SARM1

Sterile alpha and Toll/interleukin-1 receptor motif-containing protein 1

Length: 724 aa 79.4kDa

Subcellular Location: Mitochondrial Membrane

NCBI

Gene ID: 23098 **RefSeq transcripts:** NM_015077.4 **RefSeq proteins:** NP_055892.2

UniProt

Entry: Q6SZW1 **Entry Name:** SARM1_HUMAN

SARM1

Sterile alpha and Toll/interleukin-1 receptor motif-containing protein 1

Sterile Alpha Motif

SAM, structural protein motif that can **polymerize head to tail**

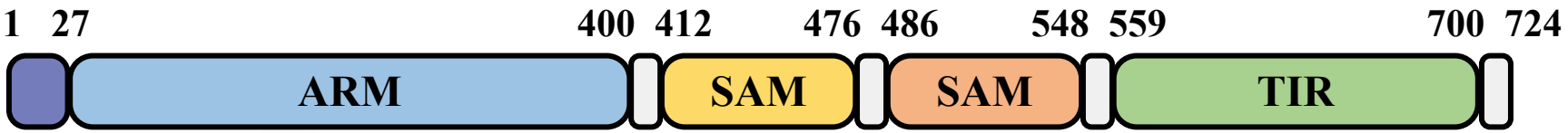
Toll/interleukin-1 receptor motif

TIR domain **degrades the essential cofactor NAD+** when activated in response to infection

SARM1

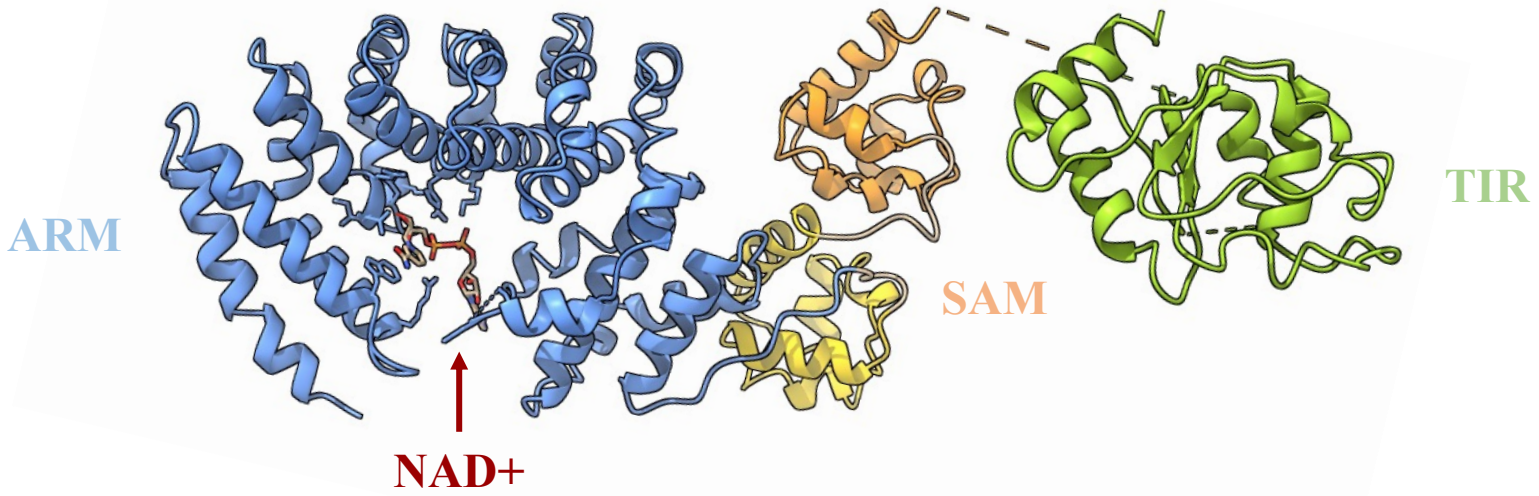
mito. local. sequence

multimerization



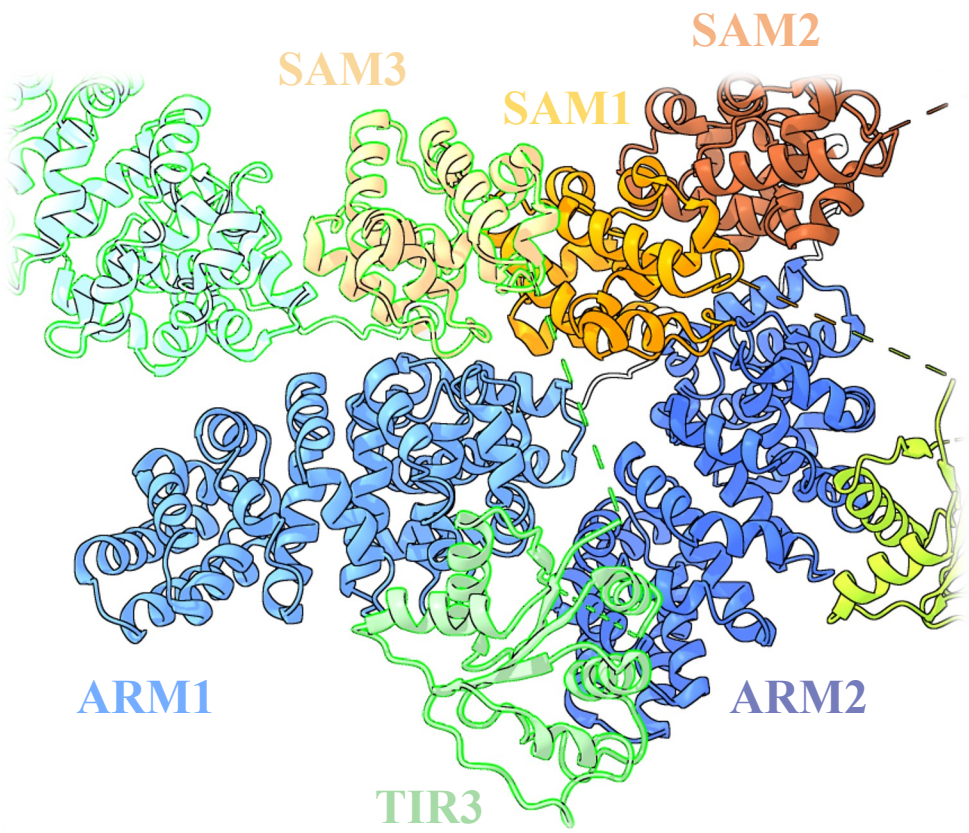
Autoinhibition of TIR domain
NMN or NAD+ binding

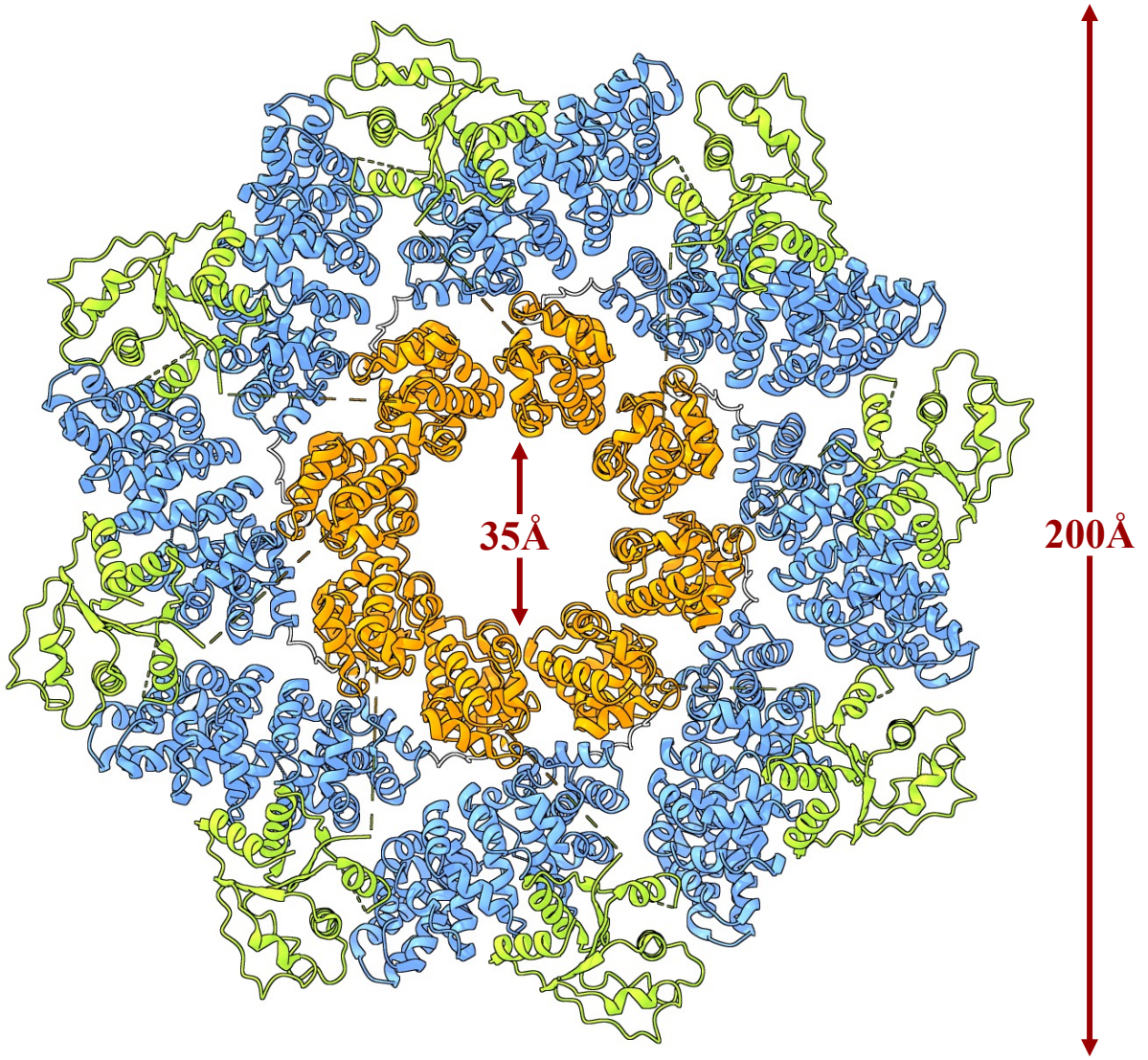
NADase activity



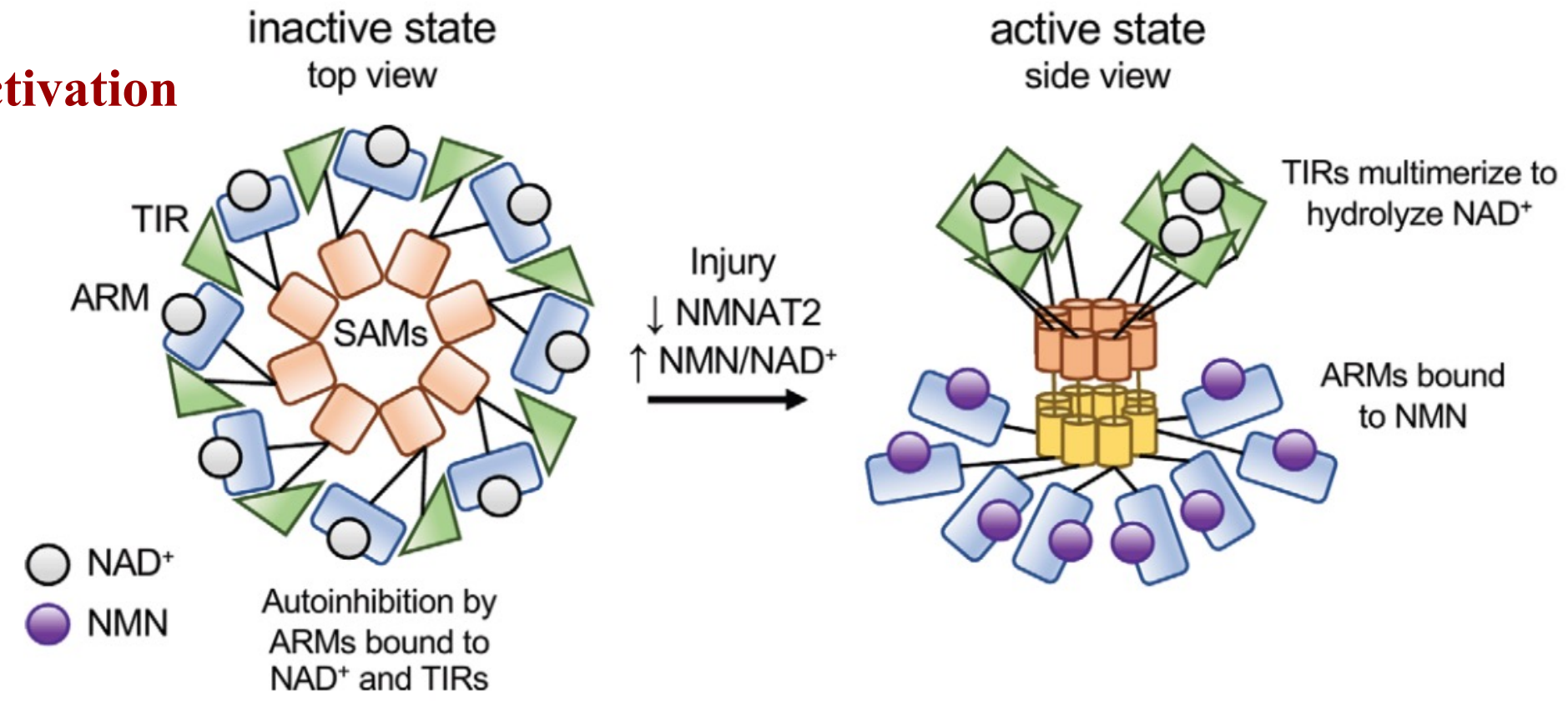
SARM1 octamer

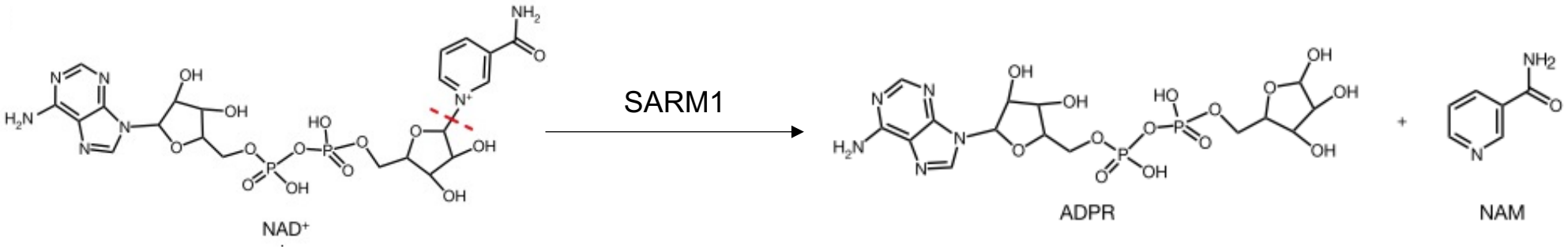
PDB: 7CM6

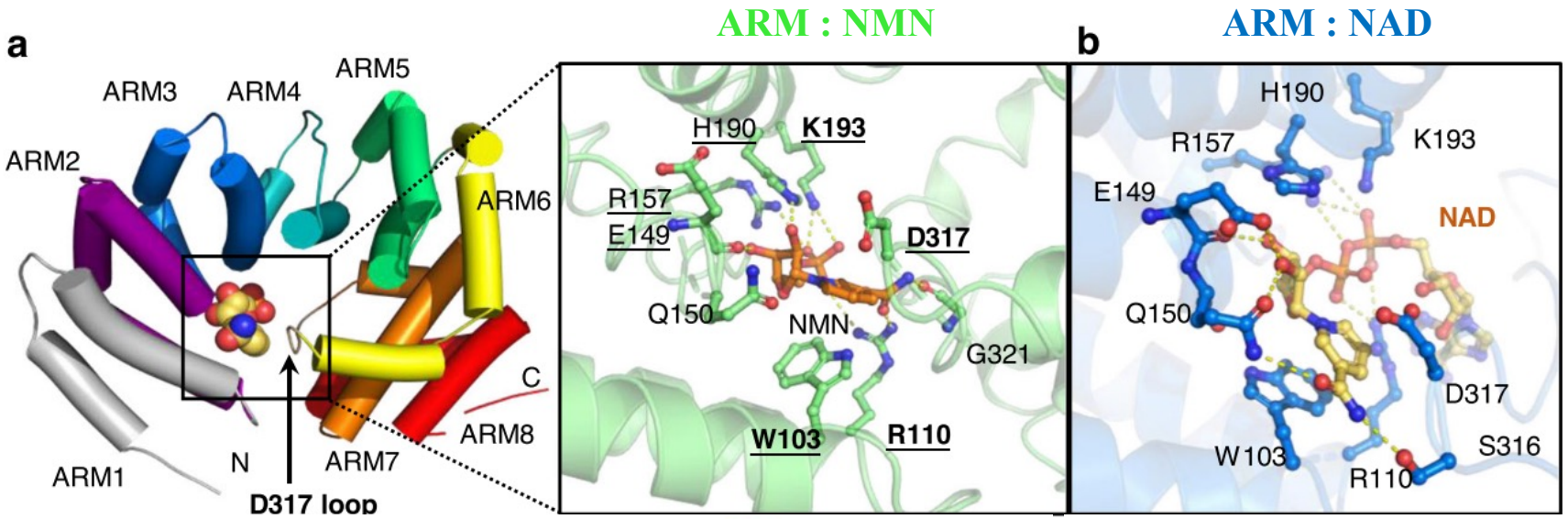


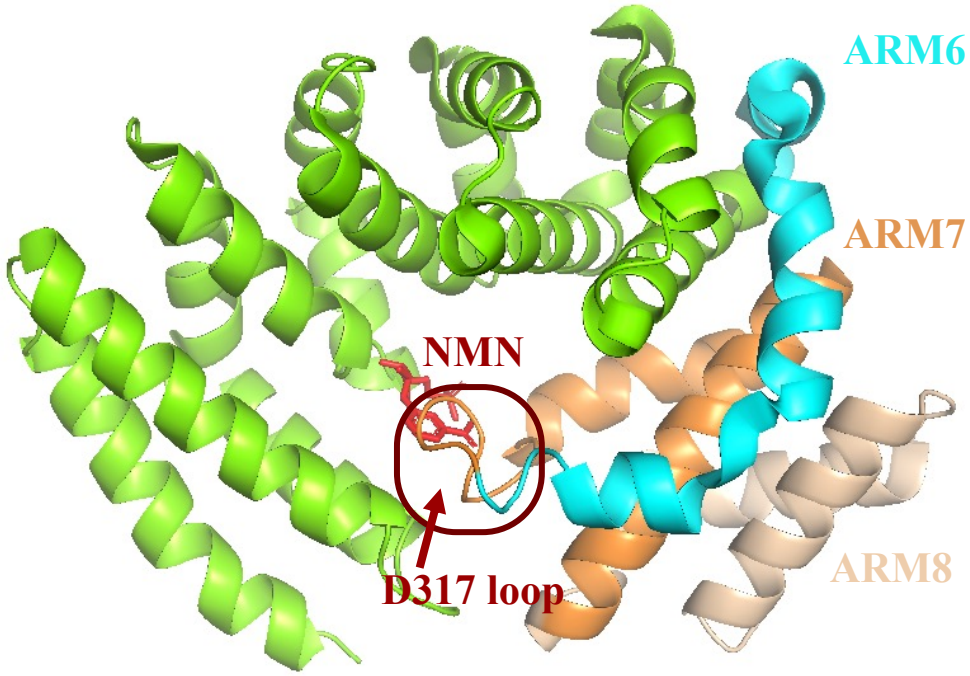


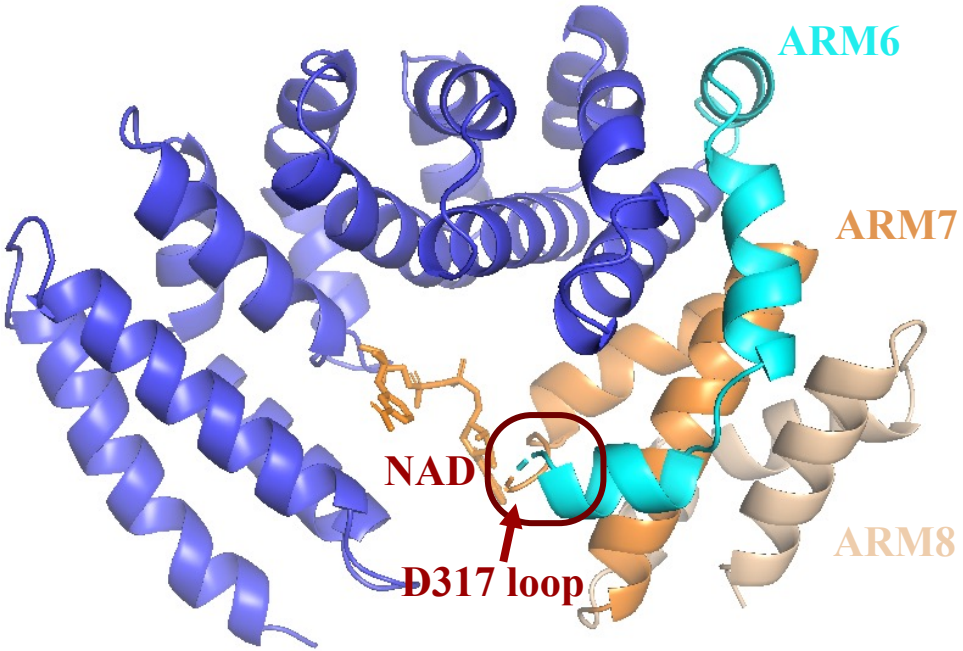
SARM1 activation



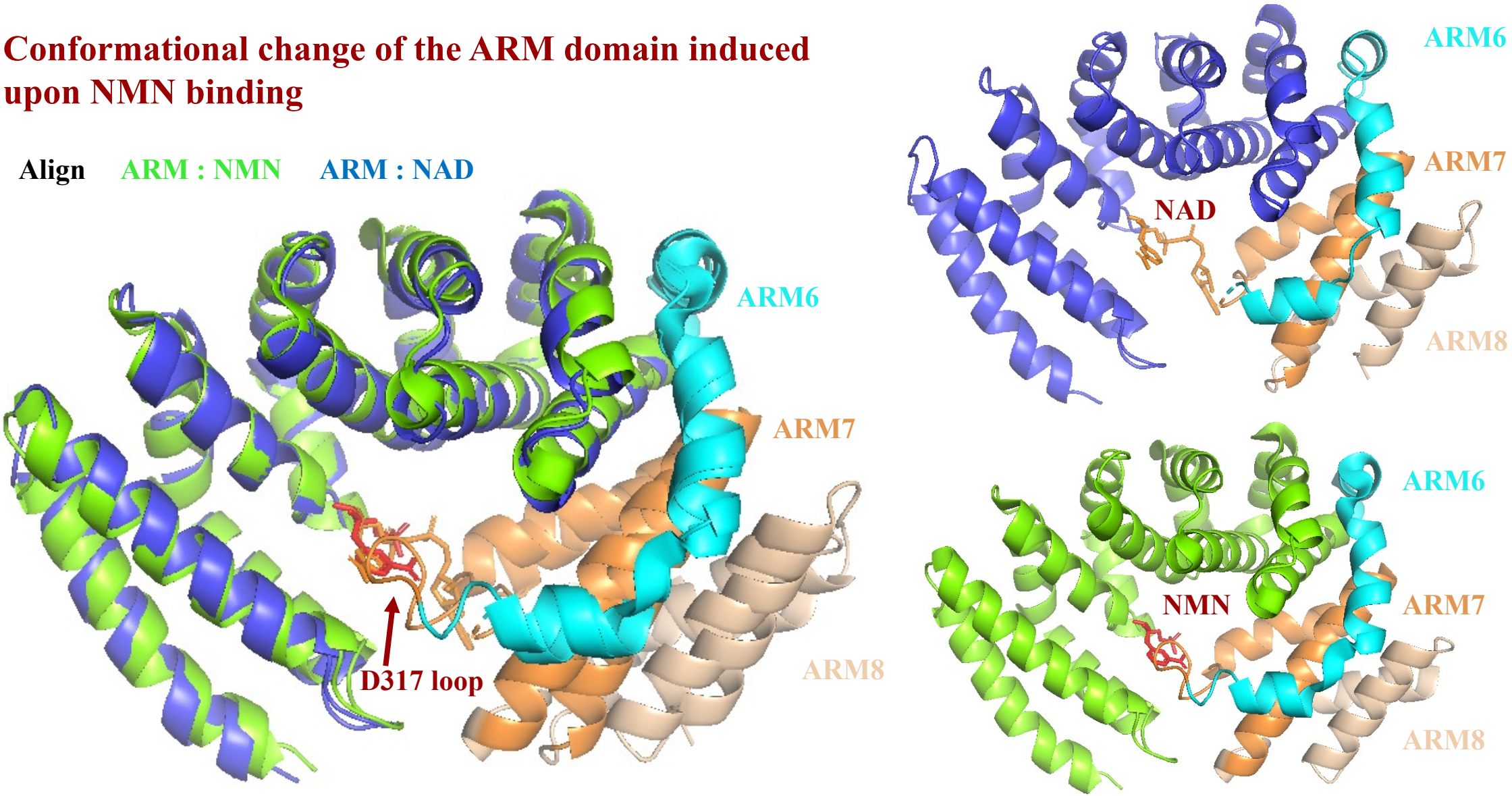


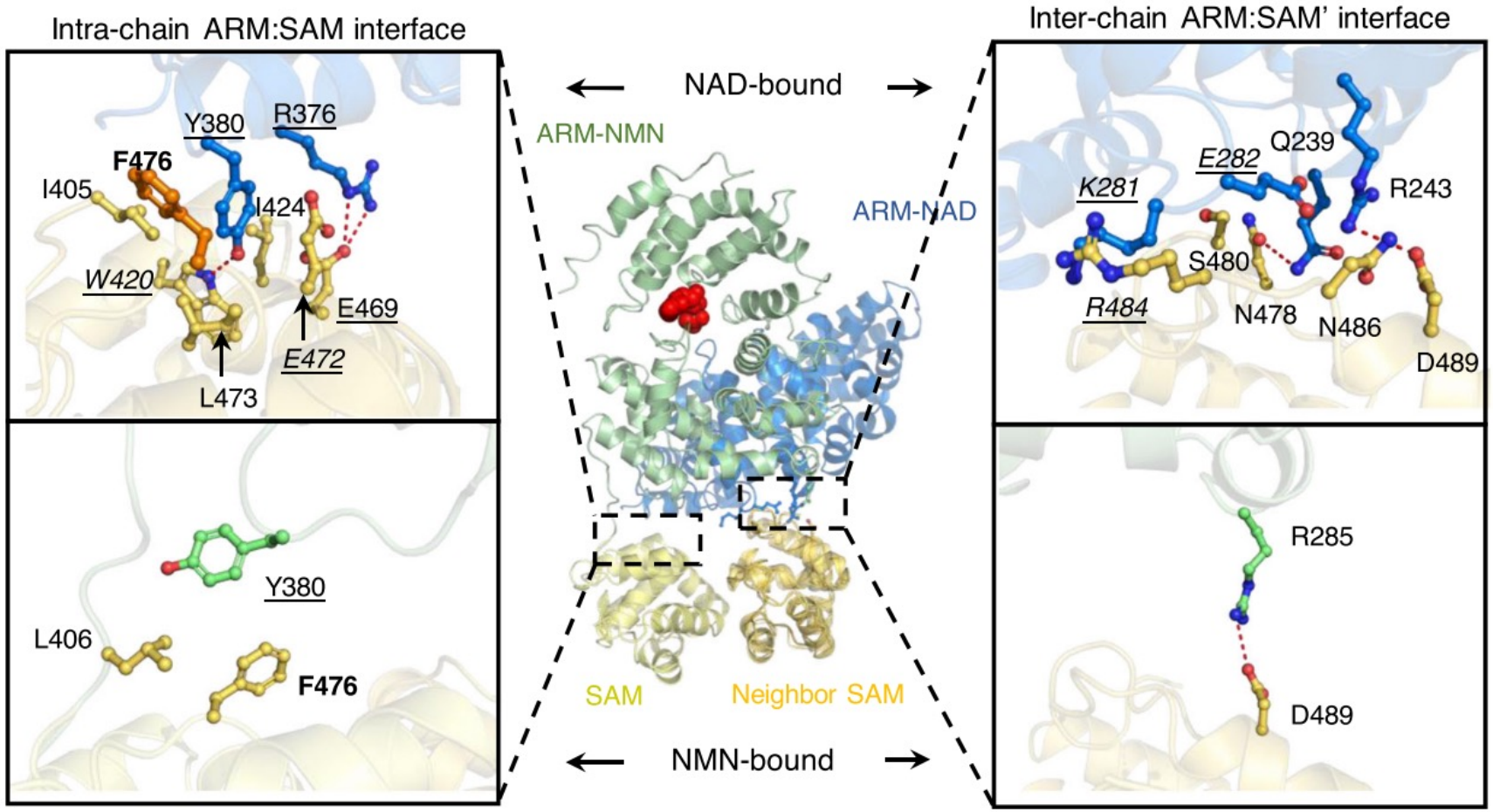

a
ARM1
ARM2
ARM3
ARM4
ARM5
ARM6
ARM7
ARM8
N
C
D317 loop
ARM : NMN
H190
K193
R157
E149
D317
Q150
NMN
G321
W103
R110
b
ARM : NAD
H190
R157
K193
E149
NAD
Q150
D317
W103
S316
R110


ARM6
ARM7
NMN
D317 loop
ARM8


ARM6
ARM7
NAD
D317 loop
ARM8

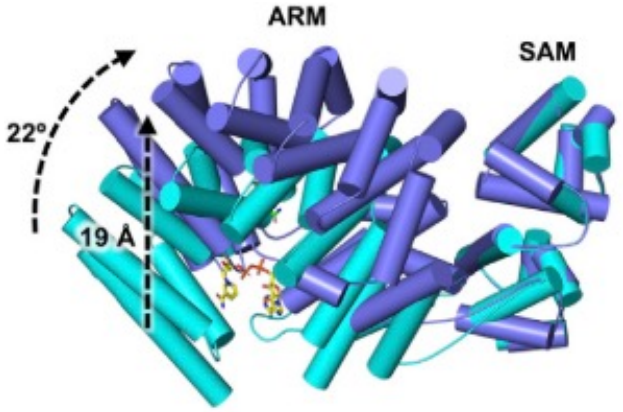
Conformational change of the ARM domain induced upon NMN binding





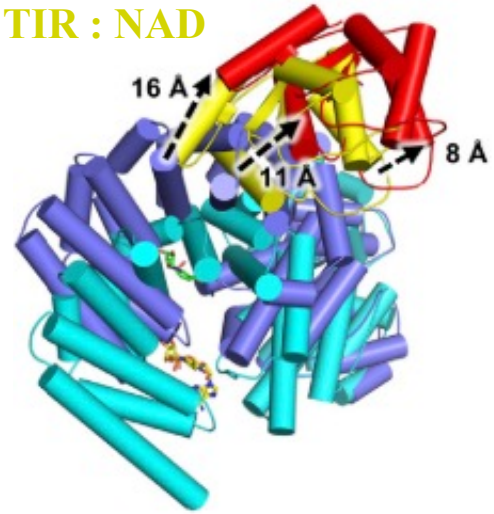
SAM-ARM : NMN

SAM-ARM : NAD

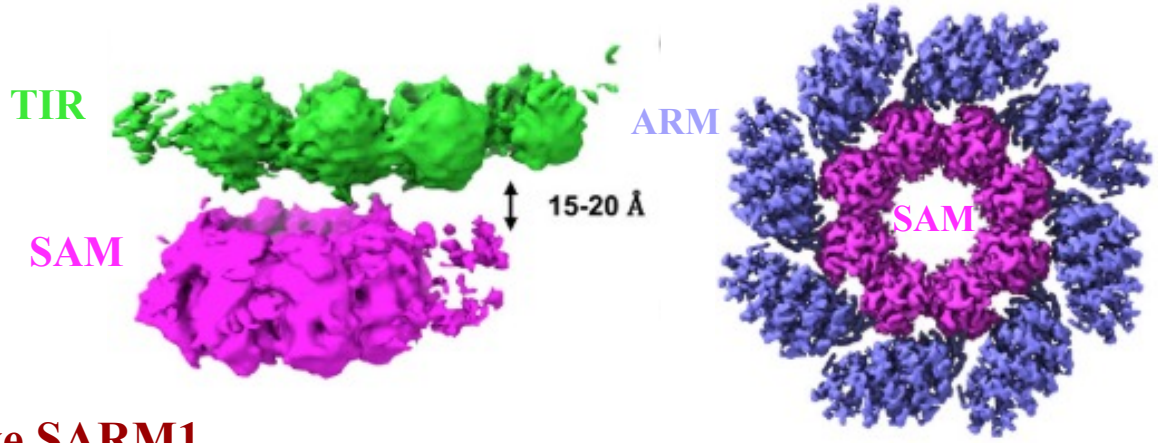


TIR : NMN (model)

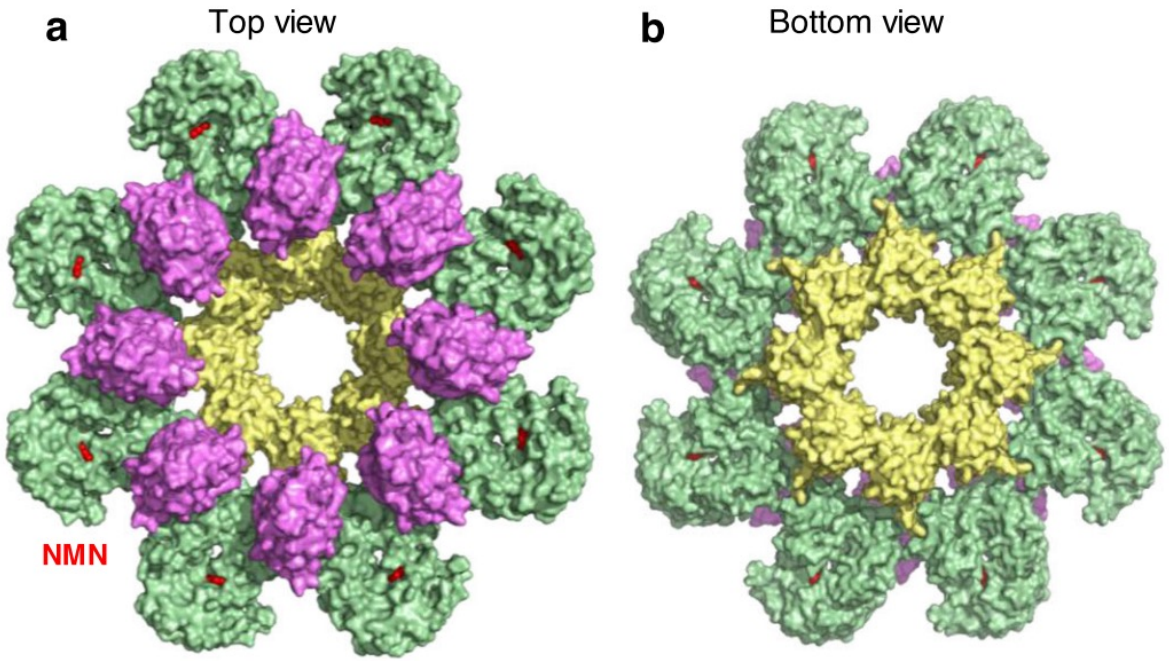
TIR : NAD

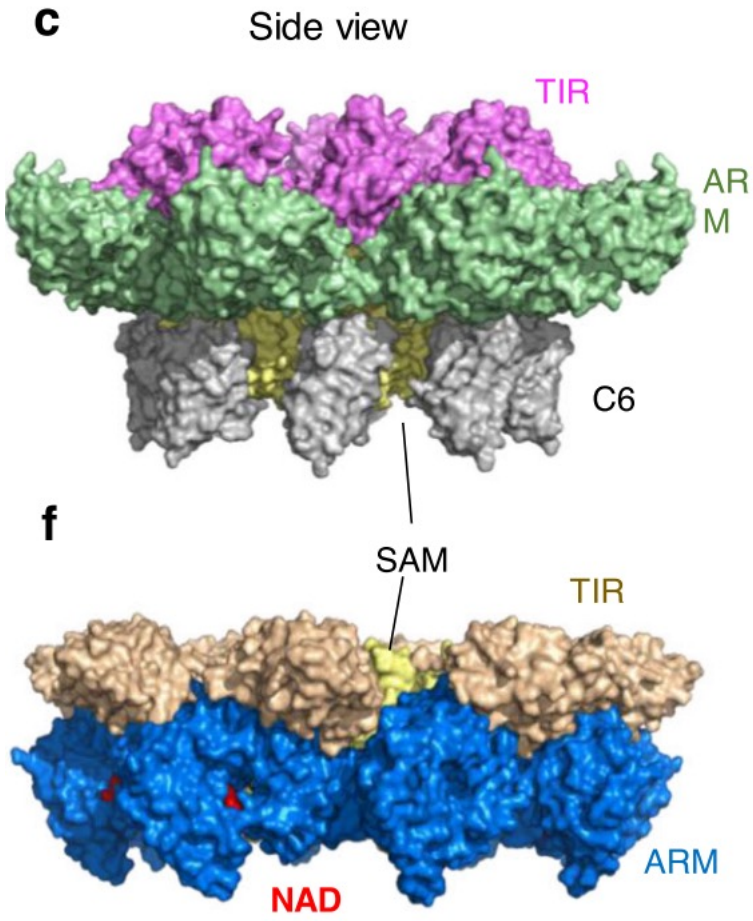


Overall structures of active or inactive SARM1



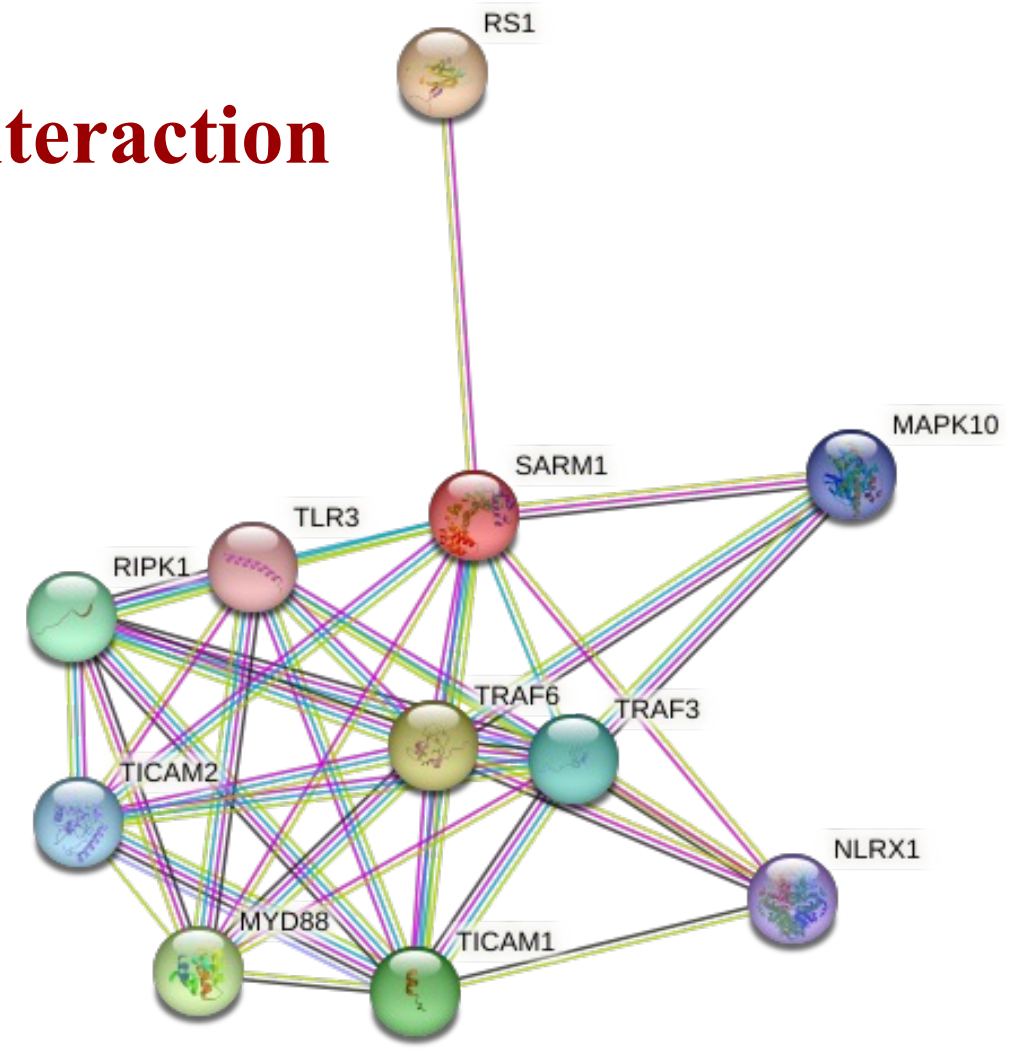
active SARM1





inactive SARM1

Interaction



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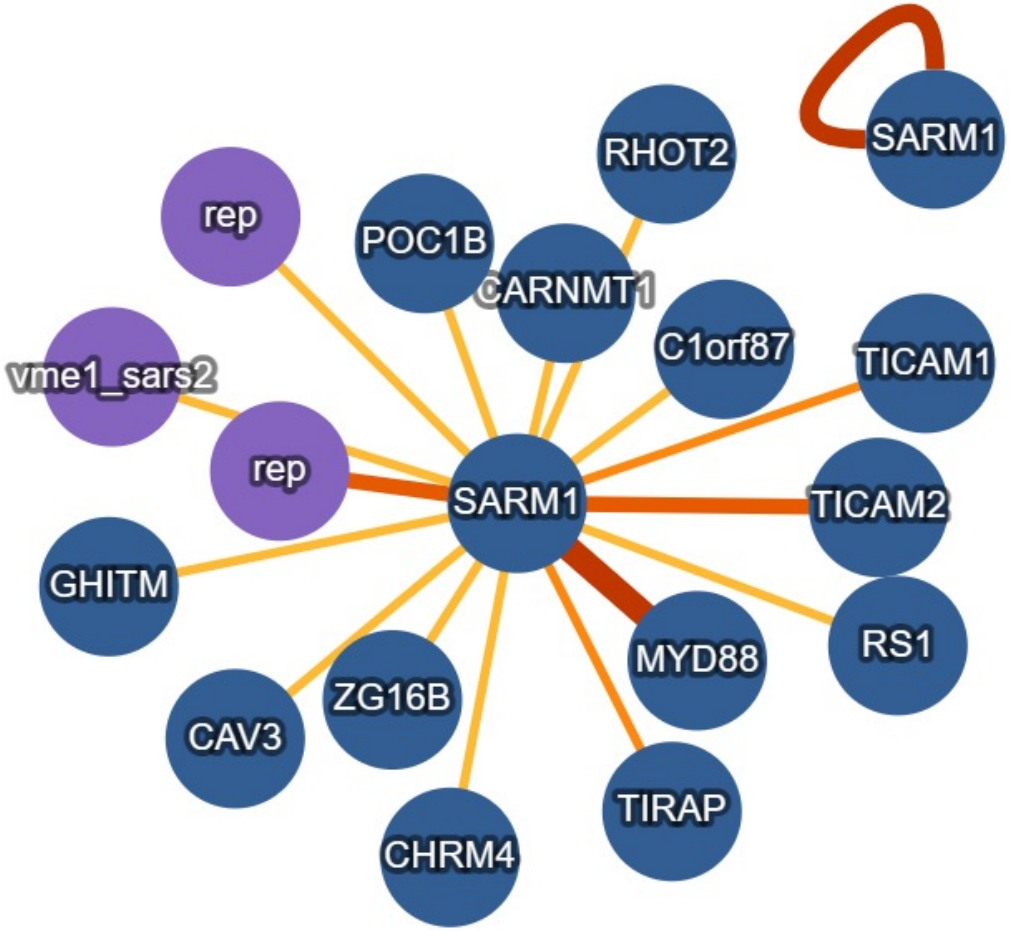


IntAct

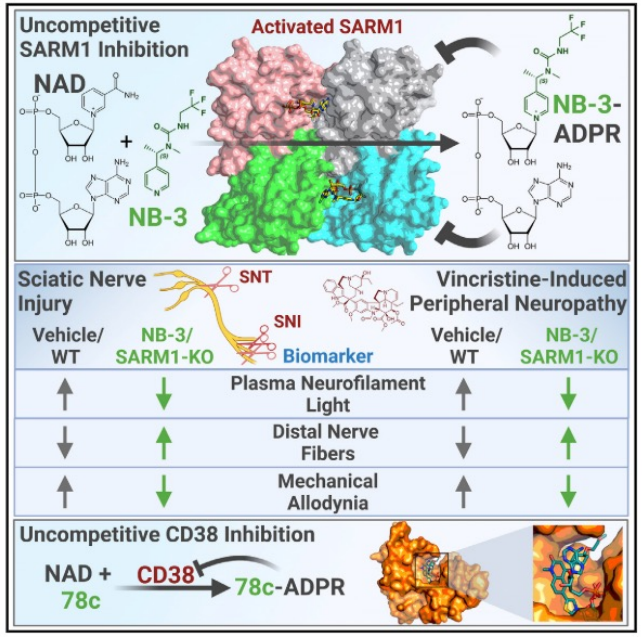
SARM1 inhibitors

Article

Neuron

Uncompetitive, adduct-forming SARM1 inhibitors are neuroprotective in preclinical models of nerve injury and disease

Graphical abstract



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In brief

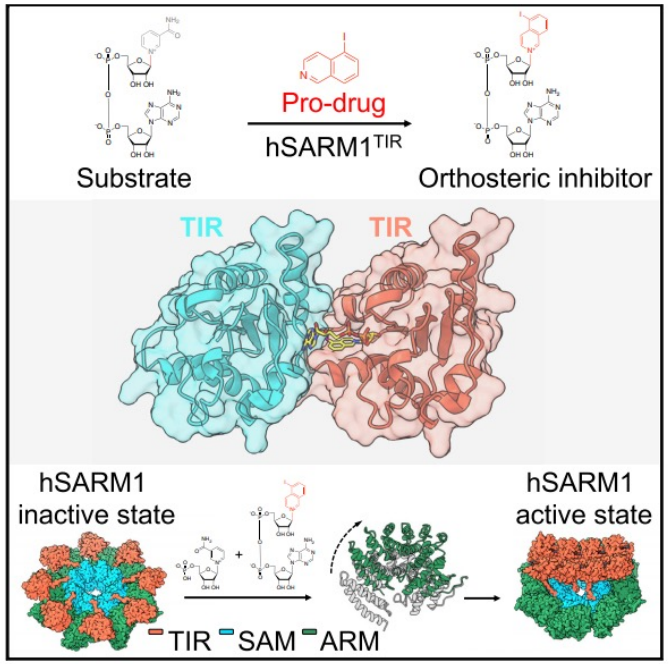
Bratkowski, Burdett, et al. elucidate the molecular basis of NAD-dependent, active-site inhibition of related NAD hydrolases SARM1 and CD38 by compounds that function by forming covalent adducts with a hydrolysis product, ADPR. They show that the SARM1 inhibitors are neuroprotective in preclinical models of nerve injury and disease.

Article

Molecular Cell

Structural basis of SARM1 activation, substrate recognition, and inhibition by small molecules

Graphical abstract



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In brief

SARM1 is an inducible pro-neurodegenerative NADase. Shi et al. show that a base-exchange reaction underlies potent orthosteric inhibition of SARM1 by a series of isoquinoline compounds. They also report crystal and cryo-EM structures of SARM1 which reveal the mechanism of substrate binding and how SARM1 is allosterically activated by NMN.