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# Friday

## Small molecule activation of valosin-containing protein (VCP)

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State of the Art: Valosin-containing protein (VCP) is a AAA+ ATPase that plays a crucial role in protein quality control and membrane trafficking/fusion. Mutations in *VCP* have been associated with frontotemporal dementia clinically. Multisystem Proteinopathy (MSP) mutations in *VCP* lead to TDP-43 aggregates and increased ATPase activity, while a Vacuolar Tauopathy (VT) leads to tau aggregates and decreased ATPase activity. Despite MSP mutations increasing ATPase activity, the unifying hypothesis is that VCP loses function in crucial proteostasis pathways, leading to neurodegenerative disease. As such, there is potential therapeutic value to compounds that increase VCP activity.

Methodology: We identified compounds that potentially increased VCP activity, validated with two orthogonal *in vitro* ATPase assays. We determined dose-dependence of all active compounds against WT VCP with and without *in vivo* relevant cofactors Ufd1 and Nploc4. We also determined effect of ATP concentration on activation and specificity to VCP by using AAA+ ATPase NSF. Walker B mutations of the D1 and D2 ATPase domains were used to determine which ATPase domain is most effected.

Results: We identified novel activators of VCP that have variable potency and maximum activation. Addition of Ufd1 and Nploc4 has variable effect on the potency of compounds. All compounds exhibit specificity for VCP over NSF. All compounds increase D2 ATPase activity with a D1 Walker B mutation. Interestingly, some compounds significantly decrease D1 ATPase activity with a D2 Walker B mutation.

Conclusions: Our data characterizes novel activators of VCP that have variable potency, maximum activity, and effect on ATPase domains.

## Conflicts of interest

None