CNM-Au8 Gold Nanocatalysis Protects Neurons Against Degeneration and Death in Multiple *in vitro* Models of Amyotrophic Lateral Sclerosis

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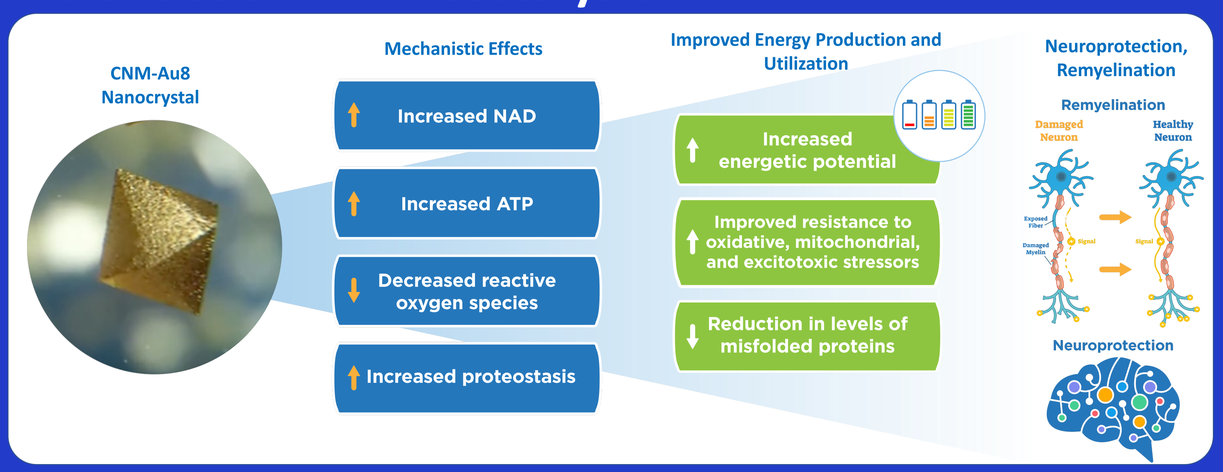
Introduction – Nanocatalysis



CNM-Au8®

- Catalytic mechanism of action enhances redox state in favor of energy production, while simultaneously lowering cellular oxidative stress
- Blood-brain barrier penetrant
- Suspension of 13 nm diameter, catalytically active, clean-surfaced, faceted gold nanocrystals
- Orally administered
- No-adverse effect level (NOAEL) nonclinical toxicology findings
- Well-tolerated; > 300 patient years of clinical exposure
- Results from Phase 2 Clinical trials presented at this meeting: Posters 034, 035, and 036. Oral P-presentation on RESCUE-ALS Clinical Trial results: Wed., Mar. 16, 11:10 AM Tennessee Ballroom.

Objective

To determine whether CNM-Au8, a catalytic suspension of clean-surfaced, faceted gold nanocrystals, promotes neuronal survival and function in multiple independent *in vitro* models of ALS.

Methods/Results

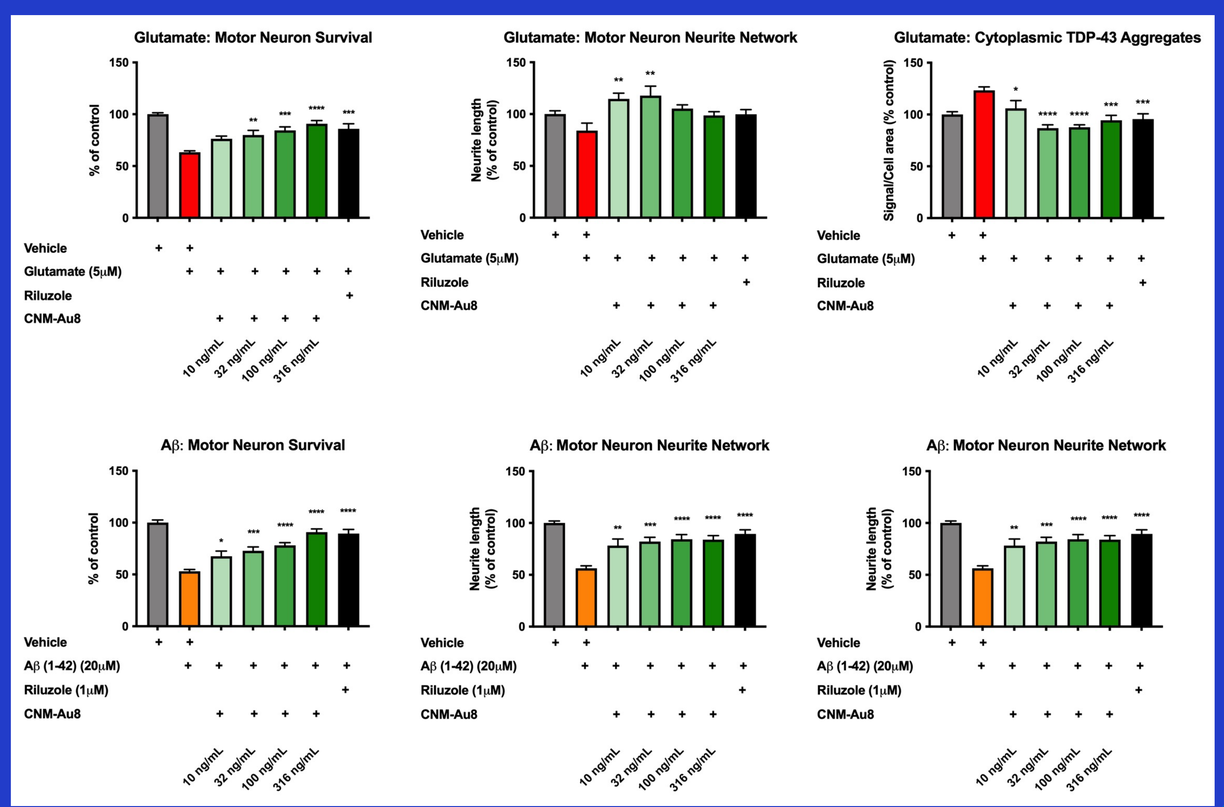
CNM-Au8's ability to promote neuronal survival and function in multiple independent *in vitro* models of ALS: (1) treatment of primary rat spinal motor neurons improves survival, preserves the neurite networks, and reduces cytoplasmic TDP-43 aggregate accumulation after either glutamate excitotoxic injury or exposure to beta-amyloid (Aβ 1-42) oligomers; (2) treatment of spinal motor neurons from transgenic SOD1^{G93A} rats protects motor neurons from death upon exposure to excitotoxic glutamate in a cAMP-dependent manner, and reduces SOD1 protein accumulation in a manner independent of cAMP; (3) treatment of human induced pluripotent stem cell (iPSC)-derived neurons from *C9ORF72* patients prevents their death in response to stress caused by mild neurotrophic factor withdrawal. Finally, we show (4) survival and neurite outgrowth of human iPSC-derived motor neurons in co-culture with toxic, SOD1^{A4V} ALS-patient derived astrocytes are substantially and dose-dependently improved with treatment of CNM-Au8.

Conclusion

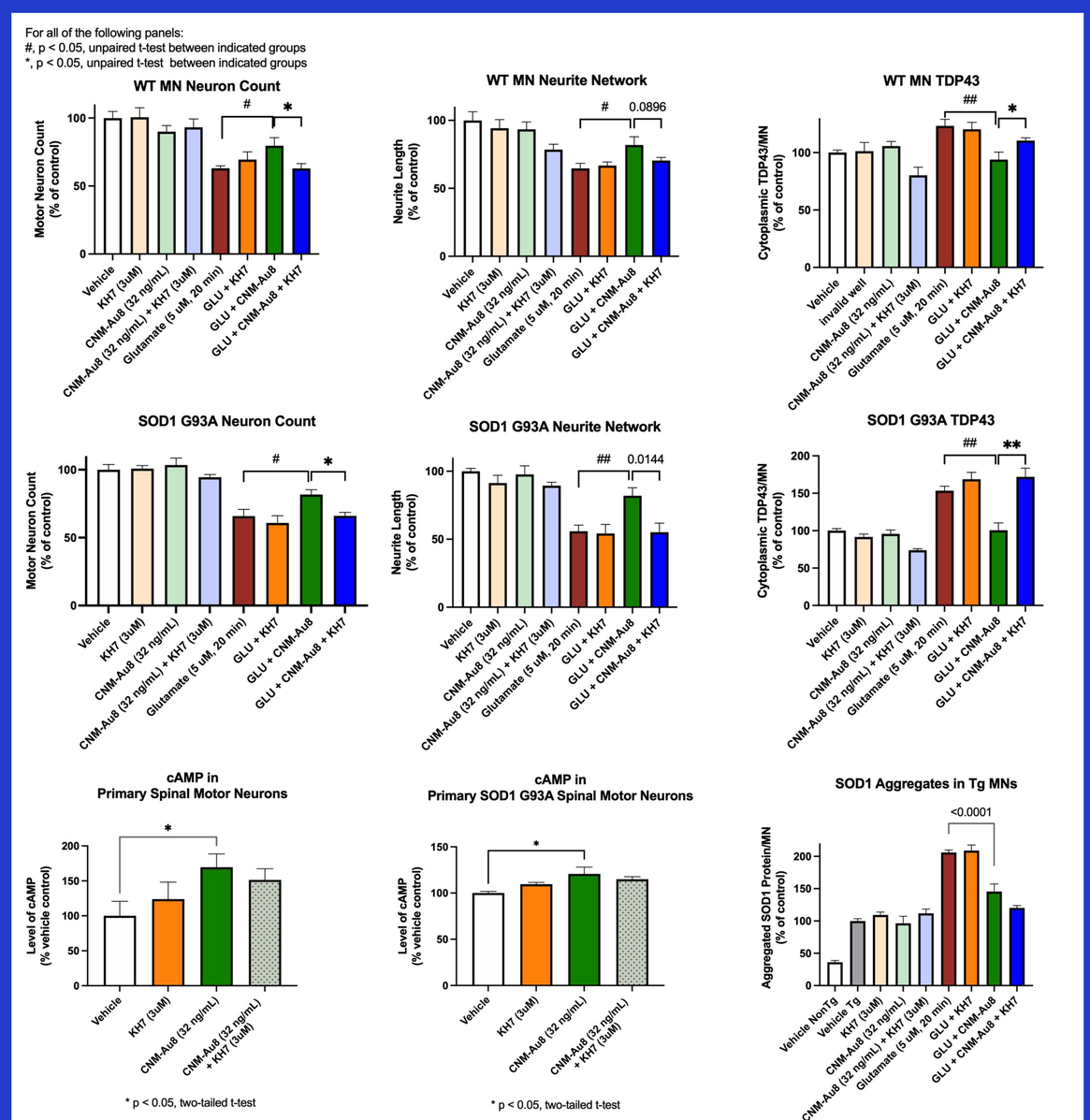
Addressing the deficits of ALS with the energetic catalyst CNM-Au8 appears to be a promising new therapeutic strategy for the treatment and disease-modification of ALS.

Results

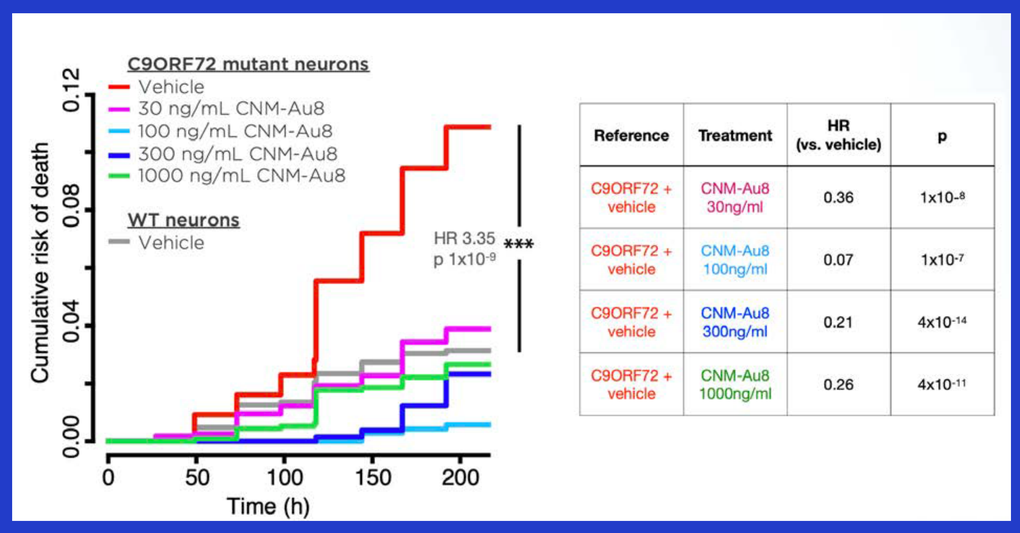
(1) CNM-Au8 Neuroprotection of Rodent Spinal Motor Neurons from Glutamate Excitotoxicity and Amyloid-Beta (1-42) Oligomers



(2) cAMP-Mediated CNM-Au8 Motor Neuron Neuroprotection of Wildtype and SOD1 (G93A) Rodent Motor Neurons

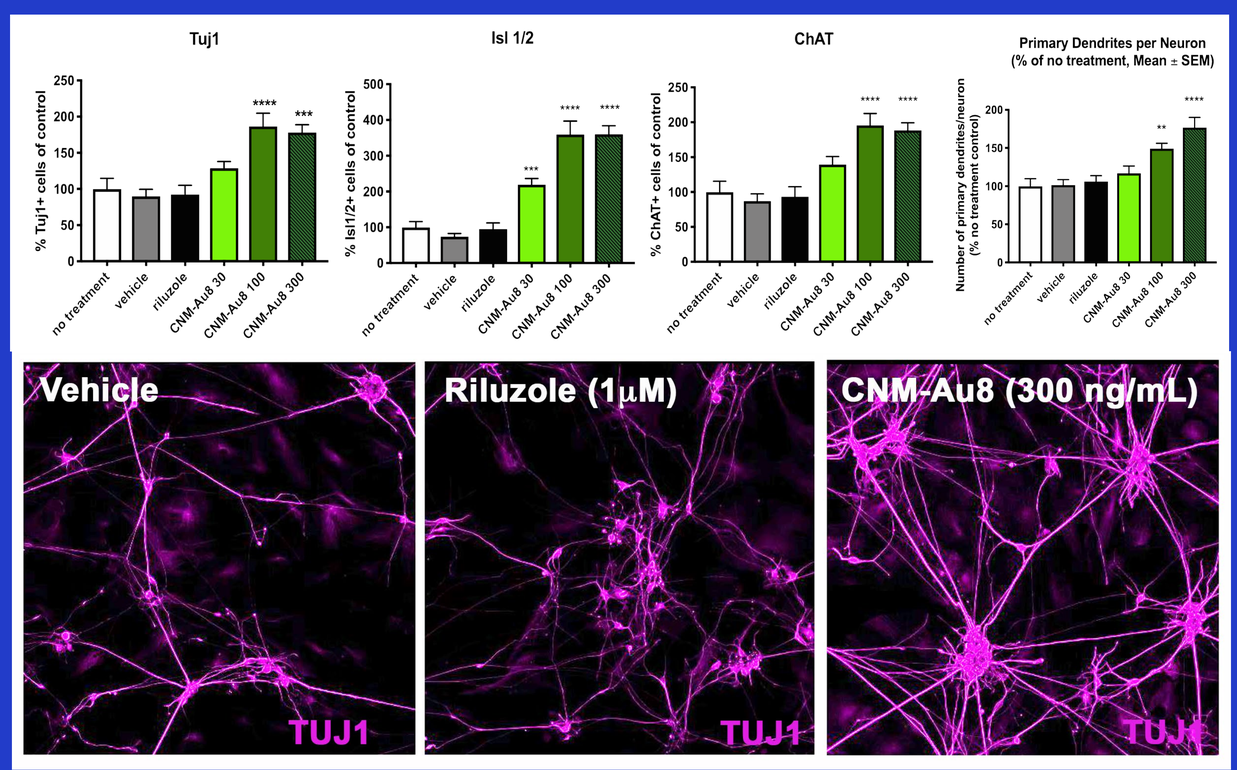


(3) CNM-Au8 Neuroprotection of Human C9ORF72 iPSC-Derived Cortical Neurons



Reference	Treatment	HR (vs. vehicle)	p
C9ORF72 + vehicle	CNM-Au8 30ng/ml	0.36	$1x10^{-8}$
C9ORF72 + vehicle	CNM-Au8 100ng/ml	0.07	$1x10^{-7}$
C9ORF72 + vehicle	CNM-Au8 300ng/ml	0.21	$4x10^{-14}$
C9ORF72 + vehicle	CNM-Au8 1000ng/ml	0.26	$4x10^{-11}$

(4) CNM-Au8 Neuroprotection of Human iPSC-derived Motor Neurons Co-Cultured with Toxic Patient iPSC-Derived Astrocytes



Acknowledgments

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