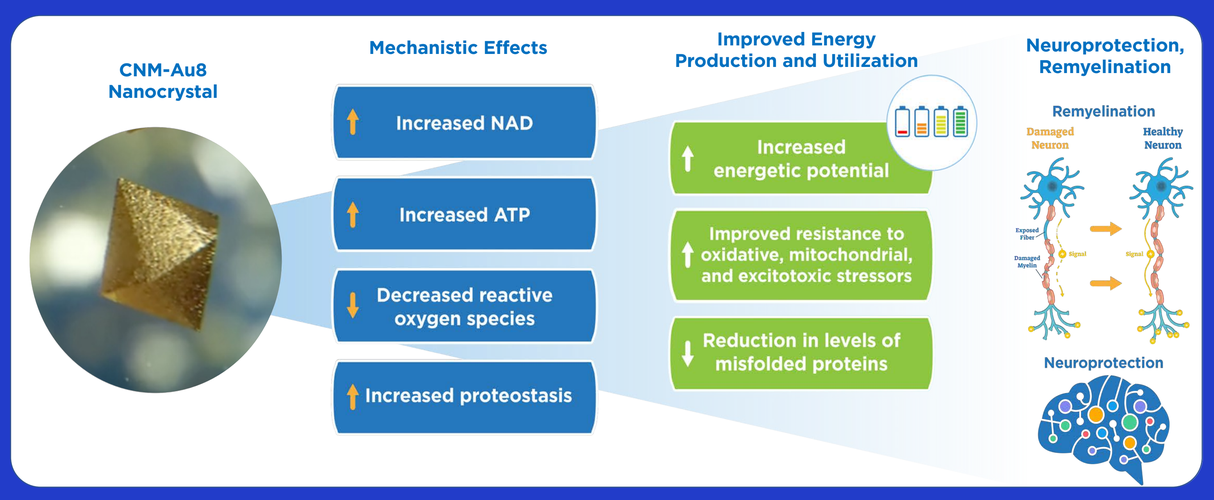
CNM-Au8 Gold Catalytic Activity Protects Neurons Against Degeneration and Death in Multiple *in vitro* Models of Amyotrophic Lateral Sclerosis

Karen S. Ho[1], Jean-Philippe Richard[2,3], Arens Taga[2], Michael Bekier[4], Alexandre Henriques[5], Noëlle Callizot[5], Michael T Hotchkin[1], Sami J Barmada[4], and Nicholas J Maragakis[2]. [1]Clene Nanomedicine, Salt Lake City, UT; [2]Johns Hopkins University, Baltimore MD; [3]currently at Reprocell, USA, Inc., Beltsville, MD; [4]University of Michigan, Ann Arbor, MI; [5]NeuroSys, Gardanne, France. karen@clene.com

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; > 400 patient years of clinical exposure
- Results from Phase 2 Clinical trials investigating CNM-Au8 are presented as sister posters at this meeting!

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

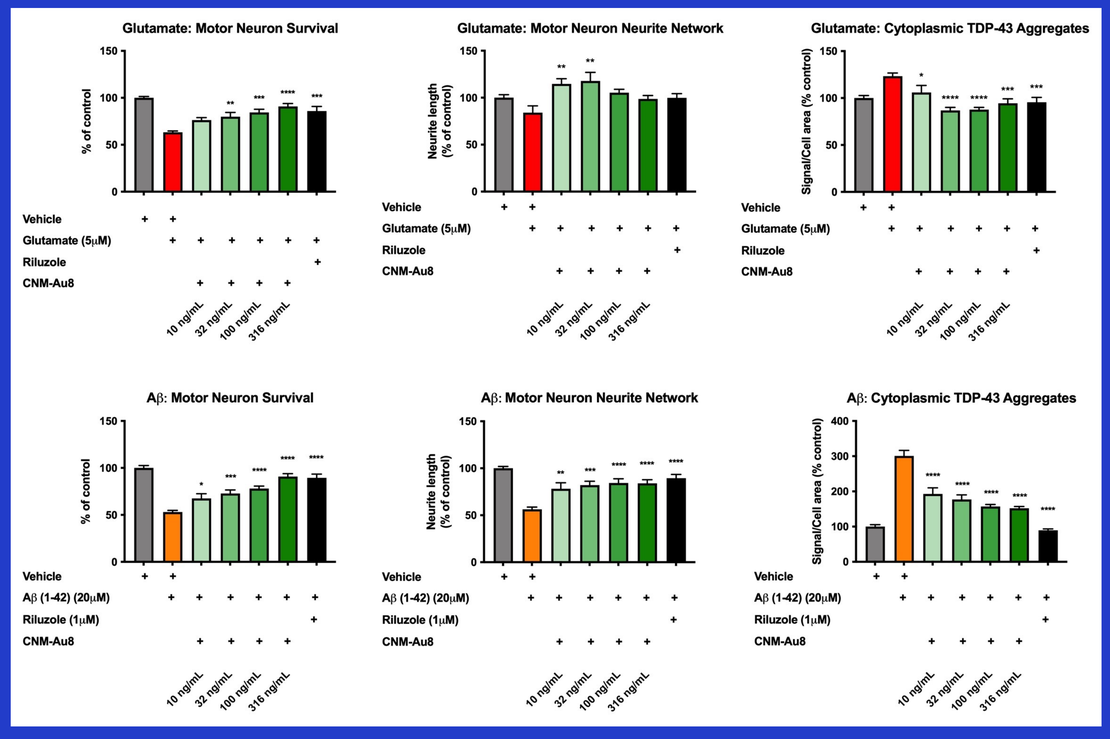
CNM-Au8's ability to promote neuronal survival and function in multiple independent *in vitro* models of ALS: (1) treatment of primary rat spinal motor neurons improves survival, preserves the neurite networks, and reduces cytoplasmic TDP-43 aggregate accumulation after either glutamate excitotoxic injury 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.

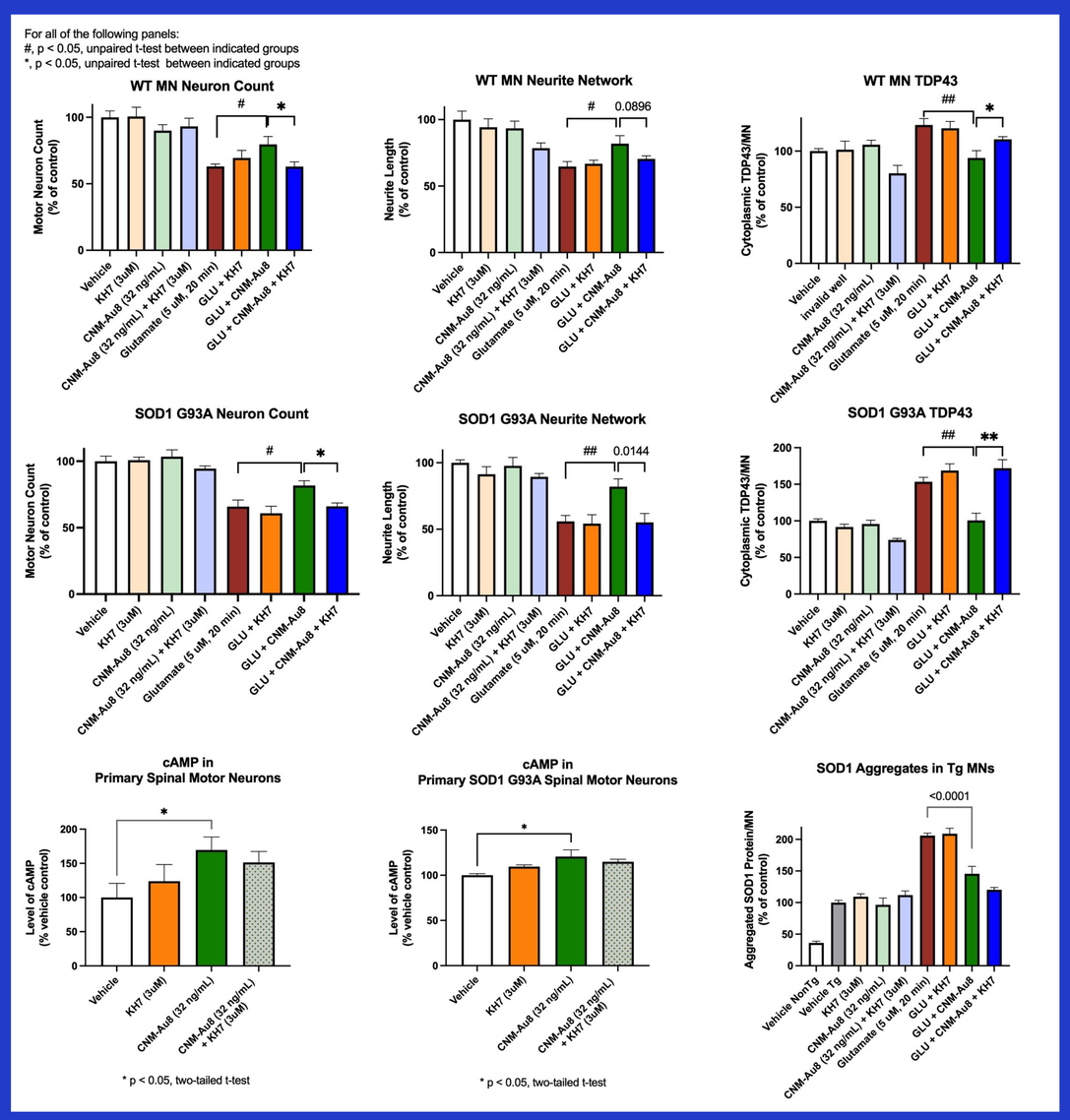
Results

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

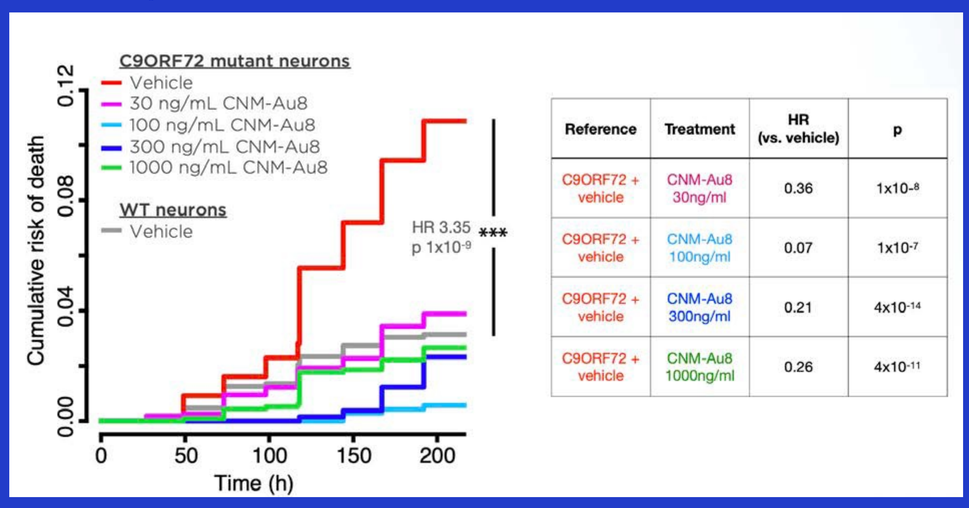


Results, cont'd.

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

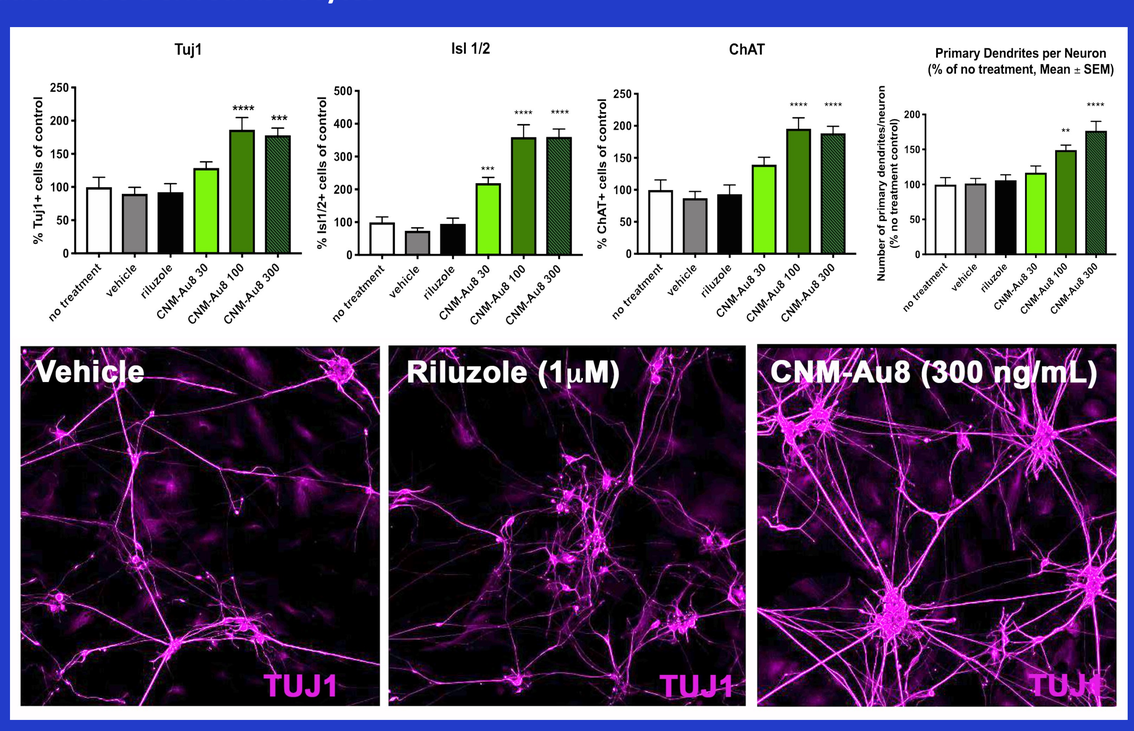


(3) CNM-Au8 Neuroprotection of Human C9ORF72 iPSC-Derived Cortical Neurons



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

We are very grateful to the individuals with ALS and healthy volunteers who donated fibroblasts, without whom the iPSC studies would not have been possible. The exceptional professional support of our colleagues at Clene has been invaluable. This study was funded by Clene Nanomedicine, Inc.