

Mitochondrial-focused therapeutics for ALS

Ronald Davis, Ph.D.¹

¹Department of Neuroscience, UF Scripps, University of Florida, Jupiter, Florida 33418

Each motor neuron (MN) in the human CNS contains thousands of mitochondria (MT) that provide many essential functions for neurons to work properly. Without a healthy MT system, neurons function at sub-optimal levels, fail, and die. Indeed, progressive dysfunction of the MT system is a major hallmark of neurodegenerative disorders, causing 3 broad MT phenotypes: (1) MT fragmentation, (2) reduced MT content, and (3) reduced MT bioenergetics. Strong evidence supports the MT Cascade Hypothesis, which envisions that other molecular and cellular pathologies arise from MT dysfunction, including degeneration of axons/dendrites, neuroinflammation, and cell death. Thus, MT-focused therapeutics offer much promise for efficacy.

We selected a few compounds from 14,400 screened using a multiplexed phenotypic, cell-based assay that captures metrics for MT health. Those selected were then tested for efficacy using human iPSC-derived lower motor neurons (MN) representing both C9orf72 and TDP43 forms of fALS, and their isogenic control MN. We identified SR24001, and analogs, as promising compounds that protect diseased MN against MT fragmentation, loss of MT content, and loss of MT function. The compounds also protect axons/dendrites from degeneration and are neuroprotective, delaying the usual death of cultured MN at culture day 18 to remarkably, longer than day 165!

In sum, we have identified a collection of small molecules based on MT-focused assays that prevent several molecular and cellular pathologies that occur in at least two forms of fALS iPSC-derived MN. Thus, these compounds may have extraordinary potential as mitochondrial therapeutics for ALS and potentially, other neurodegenerative diseases.

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Presenter Name and contact information:

Ronald Davis, Ph.D, Professor
Department of Neuroscience
UF Scripps/University of Florida
Jupiter, Florida 33418
Email: ronald Davis@ufl.edu