Beneficial Effects of High-dose Biotin (MD1003) in Models of X-linked Adrenoleukodystrophy

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Objective: Axonal degeneration is a main contributor to disability in progressive neurodegenerative diseases such as multiple sclerosis or adrenoleukodystrophy (X-ALD), in which redox homeostasis, bioenergetic failure and/or inflammation are often identified as pathogenic factors.

Background: X-ALD is a monogenic neurometabolic disorder caused by inactivation of the peroxisomal transporter of very long-chain fatty acids ABCD1. In mice, ABCD1 loss causes late onset, progressive axonal degeneration in the spinal cord's corticospinal tracts in association with locomotor disability resembling the most common phenotype in patients, adrenomyeloneuropathy.

Design/Methods: Here we are using models of X-ALD to: i) investigate if high oral doses of biotin (MD1003) are able to improve the clinical signs of the disease (axonal degeneration and locomotor deficits), and ii) elucidate by which molecular and biochemical mechanisms it operates.

Results: Our results indicate that treatment with MD1003 during 4 months normalizes ATP and mtDNA levels in the spinal cords of Abcd1-null mice. This induction of mtDNA is correlated to an increase in mitochondrial biogenesis factors and in the expression of some enzymes involved in glycolysis. Most importantly, the treatment halted the late-onset axonopathy in spinal cords of Abcd1/Abcd2-/- mice, and the associated locomotor disability as assessed by treadmill and bar-cross tests. In human fibroblasts from patients with X-ALD, MD1003 treatment (50–500 μM) was able to abolish reactive oxygen species (ROS) generated by an excess of a very long-chain fatty acid C26:0 that accumulates in patients.

Conclusions: These results show preclinical safety and efficacy in mouse models of X-ALD and reveal novel molecular mechanisms of action of MD1003 in the prevention of neurodegeneration. Future studies should address the effects of this drug on other axonopathies in which bioenergetic dysfunction and oxidative stress are contributing factors.