

PubMed

**Format:** Abstract**Full text links****OXFORD**
ACADEMICHum Mol Genet. 2014 Oct 15;23(20):5353-63. doi: 10.1093/hmg/ddu254. Epub 2014 May 22.

NIM811, a cyclophilin inhibitor without immunosuppressive activity, is beneficial in collagen VI congenital muscular dystrophy models.

Zulian A¹, Rizzo E¹, Schiavone M², Palma E³, Tagliavini F⁴, Blaauw B³, Merlini L⁴, Maraldi NM⁴, Sabatelli P⁵, Braghetta P⁶, Bonaldo P⁶, Argenton F², Bernardi P⁷.

Author information

Abstract

Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy (BM) are inherited muscle diseases due to mutations in the genes encoding the extracellular matrix protein collagen (Col) VI. Opening of the cyclosporin A-sensitive mitochondrial permeability transition pore (PTP) is a causative event in disease pathogenesis, and a potential target for therapy. Here, we have tested the effect of N-methyl-4-isoleucine-cyclosporin (NIM811), a non-immunosuppressive cyclophilin inhibitor, in a zebrafish model of ColVI myopathy obtained by deletion of the N-terminal region of the ColVI $\alpha 1$ triple helical domain, a common mutation of UCMD. Treatment with antisense morpholino sequences targeting col6a1 exon 9 at the 1-4 cell stage (within 1 h post fertilization, hpf) caused severe ultrastructural and motor abnormalities as assessed by electron and fluorescence microscopy, birefringence, spontaneous coiling events and touch-evoked responses measured at 24-48 hpf. Structural and functional abnormalities were largely prevented when NIM811--which proved significantly more effective than cyclosporin A--was administered at 21 hpf, while FK506 was ineffective. Beneficial effects of NIM811 were also detected (i) in primary muscle-derived cell cultures from UCMD and BM patients, where the typical mitochondrial alterations and depolarizing response to rotenone and oligomycin were significantly reduced; and (ii) in the Col6a1(-/-) myopathic mouse model, where apoptosis was prevented and muscle strength was increased. Since the PTP of zebrafish shares its key regulatory features with the mammalian pore, our results suggest that early treatment with NIM811 should be tested as a potential therapy for UCMD and BM.

PMID: 24852368 DOI: [10.1093/hmg/ddu254](https://doi.org/10.1093/hmg/ddu254)

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances, Grant support

LinkOut - more resources