Compound X: a novel first-in-class drug for treatment of Muscular Dystrophy

TEITUR TROPHICS

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Introduction

Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene, leading to loss of the dystrophin-glycoprotein complex. This results in **1)** membrane instability, **2)** altered energy metabolism, and **3)** impaired muscle regeneration. Muscle fiber damage increases membrane permeability, causing spill and elevation of creatine kinase (CK) into plasma, a key biomarker used to monitor disease progression and therapeutic response.

Current dystrophin-targeting therapies show limited efficacy, are suitable only for specific mutations, and comes with various side effects. An alternative approach is to upregulate utrophin, a functional dystrophin analogue that can compensate for the lack of dystrophin in DMD.

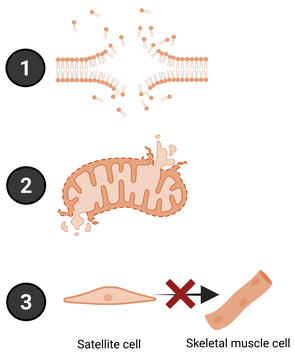
The mTOR pathway is a central regulator of muscle growth, mitochondrial function, and membrane stability, acting by increasing effectors such as utrophin, PGC1α, and myogenic transcription factors (MyoD, Myogenin). Importantly, mTOR signalling is dysregulated in DMD and related muscle-wasting disorders, making it a potential therapeutic target.

Compound X is a novel drug which has been developed by Teitur Trophics, a biotech company based in Aarhus, Denmark. The compound modulates the mTOR pathway to improve muscle function in DMD and muscle atrophy.

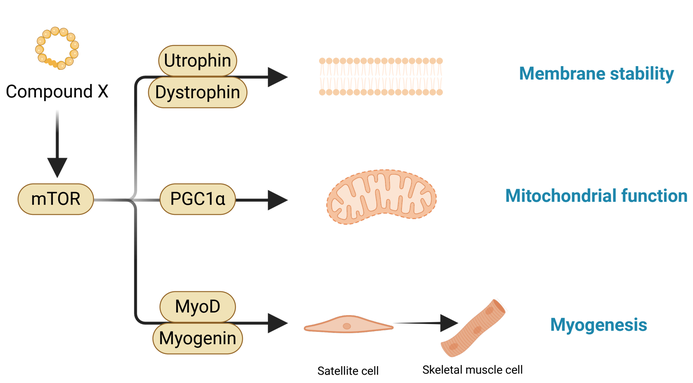
Teitur aims to select a lead candidate to enter IND development by 2026.

Statistical analyses were performed using unpaired t-tests when comparing two groups and ANOVA for comparing more than two groups. P-values: * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001. P-values below 0.05 are considered statistically significant.

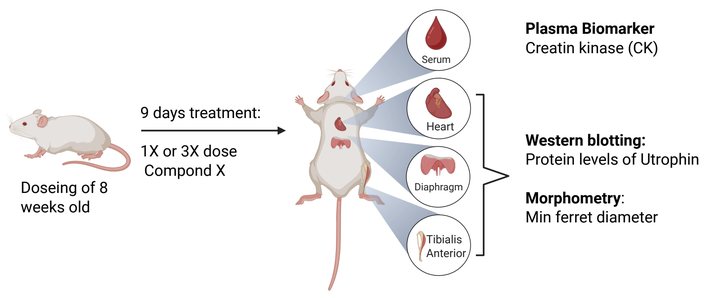
Key hallmarks in DMD



Proposed mechanism for Compound X



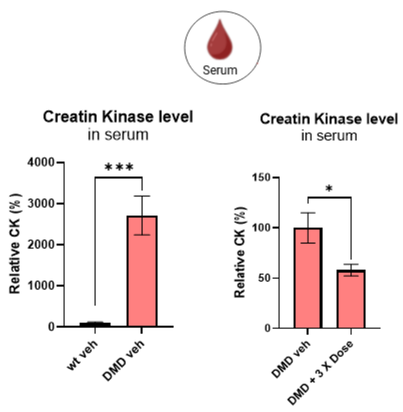
Study design to assess target engagement *in vivo*



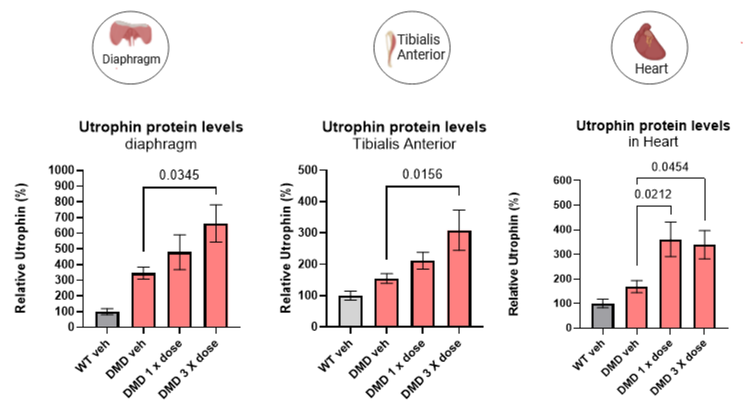
32 DMD (C57BL/10ScSn-Dmdmdx/J) male mice were divided into 4 groups; receiving either Veh (PBS), 1X or 3X dose of Compound X. 8 wild type (C57BL/10ScSnJ) treated with Veh were used as control. All mice were treated by subcutaneous administration once-daily for 9 days starting at age of 8 weeks. At termination serum and muscle tissue (Diaphragm, Tibialis Anterior and Heart) were collected. Serum was analysed for CK. Protein levels in muscle samples were analysed on western blots in house.

Compound X stabilises membrane integrity across several muscle groups and reduces serum CK *in vivo*

Key clinical biomarker

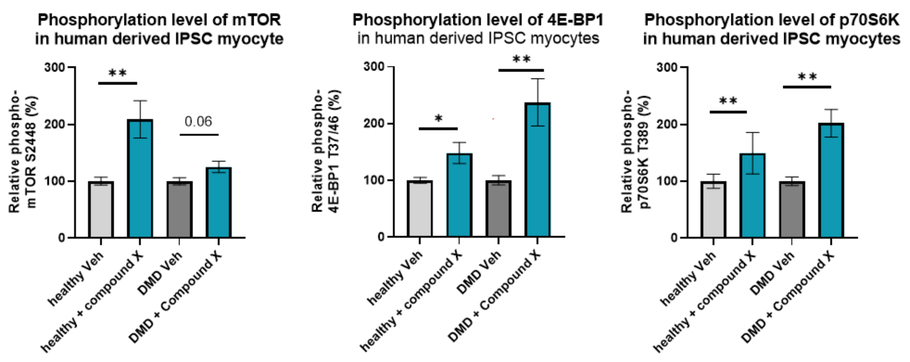


Most important therapeutic target



Compound X modulates mTOR signalling through a novel mechanism and targets key pathological hallmarks in DMD including membrane stability (Utrophin upregulation) in three muscle types: diaphragm, tibialis anterior and heart. The improved muscle membrane stability was also reflected by reduced levels of serum creatine kinase from the mdx mice.

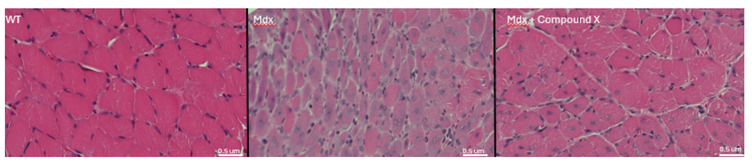
Compound X activates mTOR pathway in both healthy and DMD human iPSC-derived myocytes



mTOR signalling is dysfunctional across several muscular dystrophies and atrophies. Compound X activates mTOR by incresing phosphorylation on Ser2448 which further increases the phosphorylation level on 4E-BP (T37/46) and p70S6K (T389), which are downstream targets of mTOR.

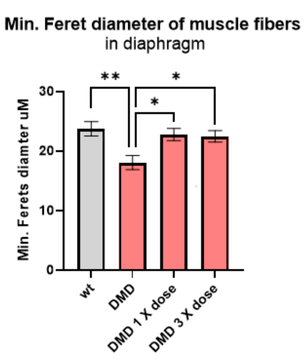
Method: ioSkeletal Myocytes from Heathy or DMD Del Ex44/Y were treated with Compound X for 24 hours and subsequenlty lysed. Protein levels were analysed by western blotting.

Compound X improves muscle morphometry in mdx mice

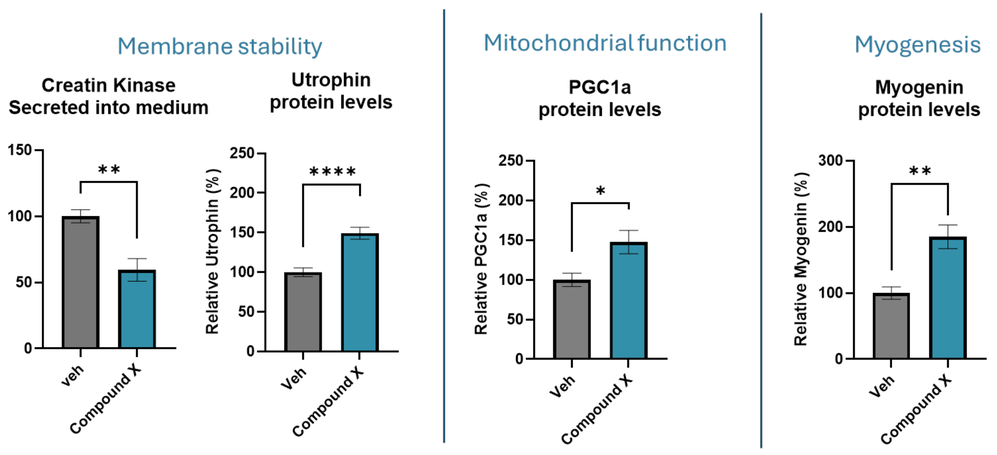


Compound X increases minimum feret diameter in diaphragms of mdx mice (preliminary)

Method half of diaphragm from each animal was formalin fixed, paraffin embedded, sliced and stained with Hematoxylin and Eosin (H&E). Images were obtained using the Slide Scanner, Upright Widefield, AxioScan 7, Zeiss. Morphometry analysis was conducted using two combined python scripts designed to automatically and unbiased prepare and calculate the min ferret dimeters of each muscle fibre recognised by the cellpose model cpsam available on github https://www.cellpose.org, Pachitariu et al..



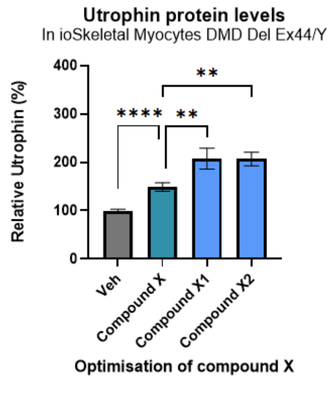
Compound X improves key aspects of DMD in human iPSC-derived myocytes with DMD (ex44/Y)



Compound X increases Utrophin levels in DMD myocytes and reduce membrane leakiness measured by Creatine Kinase spill into the medium. Compound X also increases PGC1a and myogenin.

Method: ioSkeletal Myocytes DMD Del Ex44/Y were treated with compound x for 24 hours, then medium was collected and analysed using commercial ELISA kit (SEA109Hu). Protein levels were analysed by western blotting.

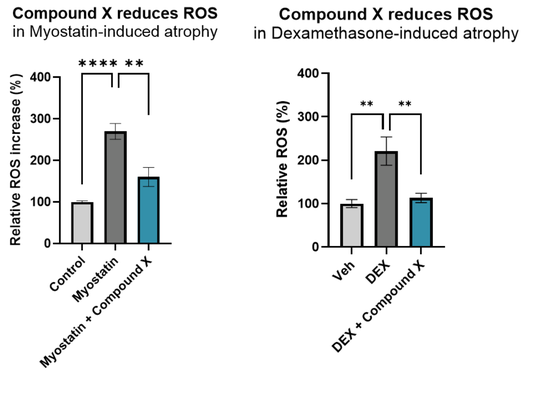
Optimization



Compound X has been optimised to further increase Utrophin levels in DMD myoctes.

Method: ioSkeletal Myocytes DMD Del Ex44/Y were treated with Veh or similar dose of either of the three variants of compound X (X, X1 or X2). The cell lysate was analysed for utrophin levels on traditional western blots.

Expanded use in Muscle Atrophy



Compound X reduces ROS levels measured in both myostatin and dexamethasone (DEX) induced muscle atrophy in human myocytes.

Method: ioSkeletal Myocytes treated with 5 µg/mL Myostatin or 50 uM dexamethasone (DEX) for 48 h with or without compound X. ROS was measured using the DCFDA/H2DCFDA Cellular ROS Assay Kit (ab113851).

AFFILIATIONS

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DISCLAIMER

Compound X is an investigational new drug developed by Teitur Trophics and has not been approved by the FDA or EMA for any use.