

Protein Based Treatment for Duchene Muscular Dystrophy and Cancer

(No. T4-1913)

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Overview

Duchenne muscular dystrophy (DMD) is a disease that affects approximately 1 in 3,500 boys with a life expectancy of ~26 years. Newly approved FDA treatments are designed to treat specific mutations that account for only 25% of the patients, leaving an unmet need for an effective treatment for the clinical pathologies of the disease. Many of these pathologies are caused by dysregulation of the extracellular matrix (ECM). The lab of prof. Irit Sagi has developed an antibody-like inhibitor for a key ECM remodeling enzyme. This inhibitor is specific, stable and was proved beneficial in a DMD mouse model.

Background and Unmet Need

Duchenne muscular dystrophy (DMD) is a disease that causes progressive muscle weakness, loss of skeletal and heart muscle tissue, degeneration, and eventual death. Muscle weakness is usually noticeable by 3 or 4 years, and early signs may include delayed ability to sit, stand, or walk and difficulties learning to speak. DMD is caused by mutations in the DMD gene. It is inherited in an X-linked recessive pattern; therefore, it primarily affects males, with a prevalence of approximately 1 in 3,500 boys. However, it may also occur in people who do not have a family history of DMD. While there is no known cure for DMD, there are treatments that can help control symptoms. Corticosteroids, such as prednisone and deflazacort (Emflaza), can help muscle strength and delay the progression of certain types of muscular dystrophy. However, prolonged use has substantial side effects. The recently approved FDA drugs for DMD, Vilepso, Vyondys 53, and Exondys 51, are antisense oligonucleotides, each designed to treat a specific confirmed mutation of the DMD gene. Consequently, less than one-quarter of DMD patients may respond to these treatments, and studies are ongoing to demonstrate their clinical benefit ^{1,2}.

Therefore, there is a need for an effective treatment for the clinical pathologies of DMD. Many of the DMD pathologies are caused by dysregulation of the extracellular matrix (ECM), mostly collagen, which leads to restricted muscle repair and regeneration, enhancement of inflammation and exacerbation of disease progression.

The Solution

Prof. Irit Sagi and her team developed a specific protein inhibitor for Lysyl oxidase (LOX), a key ECM remodeling enzyme that catalyzes the final step in collagen crosslinking during fibrosis, which is significantly overexpressed in DMD patients.

Technology Essence

LOX is naturally synthesized and secreted as a 50-kDa inactive proenzyme, which is processed by proteolytic cleavage to a functional 32-kDa enzyme (LOX) and an 18-kDa prodomain (LPD). A stable form of the lysyl oxidase prodomain was fused to an Fc antibody fragment (Fc-LPD) to generate a specific and stable inhibitor for LOX. Fc-

LPD is expressed in dimer formation, creating a minimized antibody-like inhibitor. Fc-LPD affinity and stability measurements were performed against LOX, determining the binding affinity ($EC_{50}=274\text{nM}$) and dissociation constant ($K_d=32\text{nM}$). Preliminary in vivo studies in a DMD mouse model system showed improvement in functional tests, such as rotarod running and hanging tests as well as inhibition of fibrosis accumulation and promotion of normal collagen organization (Figure 1).

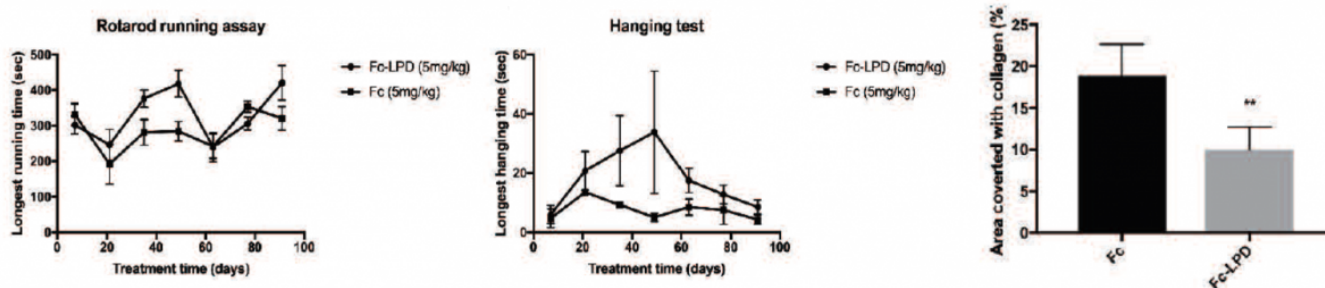


Figure 1-In vivo evaluation of DMD muscle fibrosis after treatment with Fc-LPD.

Applications and Advantages

- A specific and stable protein inhibitor that directly treats DMD pathologies by minimizing tissue fibrosis.
- Demonstrated functional improvement in a DMD mouse model.
- The inhibitor can potentially be used by all DMD patients, regardless of the specific mutation that causes the disease.
- The inhibitor only affects the extracellular LOX without affecting its intracellular activities, which are needed for muscle regeneration.

Development Status

The protein inhibitor was purified and analyzed in vitro, proved to be specific, stable, and with high binding affinity. It was also tested in vivo on an MDM mouse model system, where it significantly inhibited fibrosis accumulation and promoted normal collagen organization.

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Patent Status



PCT Published: Publication Number: WO 2023/218450 PCT Published: Publication Number: WO2023/156999 USA
Published: Publication Number: 2022-0049236-A1
