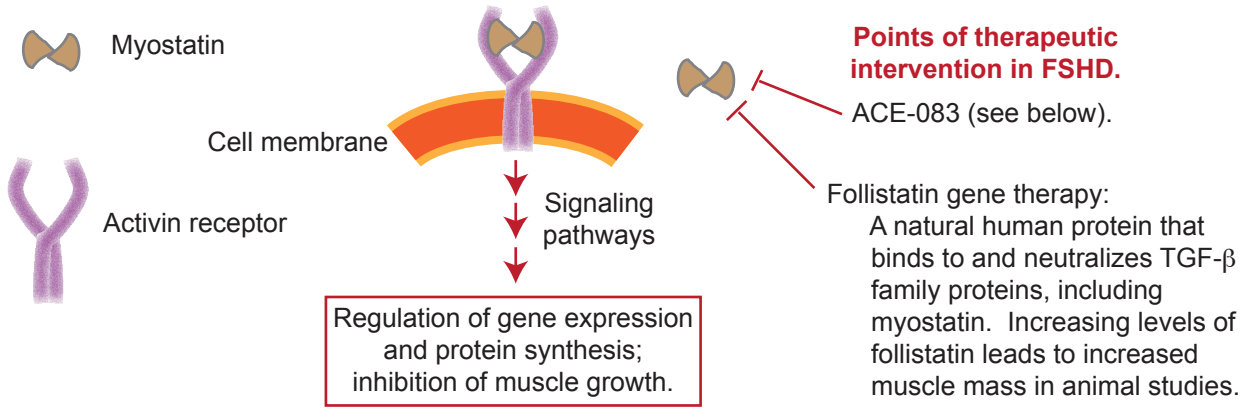
FSHD Therapeutic Approaches: Myostatin inhibition

Myostatin inhibition is an approach to treat muscle diseases by "tricking" your body into making more muscle mass.

What is myostatin?

Myostatin (aka GDF8, growth and differentiation factor 8) is a protein that is secreted by myocytes (differentiating muscle cells) and functions to inhibit muscle growth. Individuals (and animals) with mutations resulting in less myostatin have more muscle mass and are stronger.

Thus, myostatin is a therapeutic target for muscular dystrophy; however, inhibiting myostatin activity does not treat the root cause of disease; the accumulated muscle mass will have the same mutation, or defect, as untreated muscle.



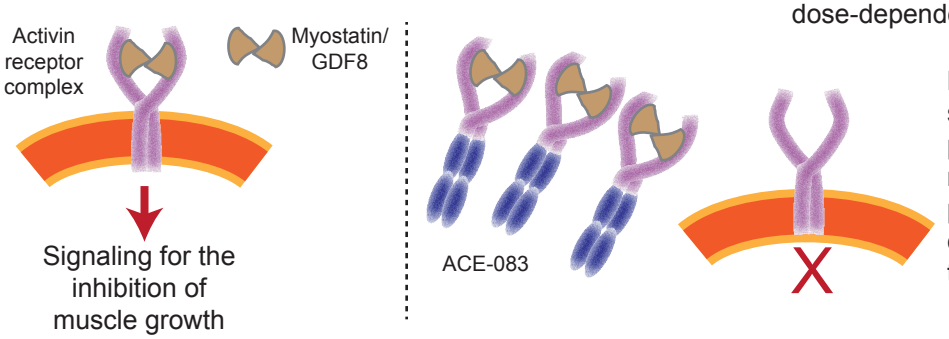
A083-02 Phase 2 clinical trial for FSHD (NCT02927080)

Evaluated ACE-083, a locally acting protein therapeutic that binds myostatin AND other negative regulators of skeletal muscle growth with the intent to locally increase muscle mass and strength.

Glasser *et al.* (2018) *Muscle Nerve* 57:921-26.

Study A083-02 was a multicenter, Phase 2 study to evaluate the safety, tolerability, pharmacodynamics (PD), efficacy, and pharmacokinetics (PK) of ACE 083 in patients with FSHD to be conducted in two parts. Part 1 is open-label, dose-escalation and Part 2 is randomized, double-blind, and placebo-controlled.

Terminated in 2019 as it did not achieve functional secondary endpoints. However, it was well-tolerated and led to dose-dependent increases in muscle volume.



Localized ACE-083 binds to the soluble myostatin/GDF8, which prevents its binding to the activin receptor complex, and thereby preventing the negative intra-cellular signaling and leading to enhanced muscle growth.

Potential use as a combinatorial FSHD treatment with any number of *DUX4* inhibition strategies.