A Myostatin Inhibitor Enhances the Repair and Regeneration of both Muscle and Bone in a Model of Deep Penetrant Musculoskeletal Injury

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INTRODUCTION:

Myostatin (GDF-8) suppresses muscle growth and development, and myostatin deficiency increases muscle mass (Fig. 1). Blocking myostatin enhances muscle regeneration,[1] and congenital absence of myostatin has been shown to increase size and strength of the fracture callus following osteotomy.[2]

Active myostatin can be inhibited by a recombinant propeptide (Fig. 2). We used a fibula osteotomy model in normal mice treated with a recombinant myostatin propeptide (three injections over 14 days) to test the prediction that myostatin inhibitors can improve bone repair and soft-tissue healing.

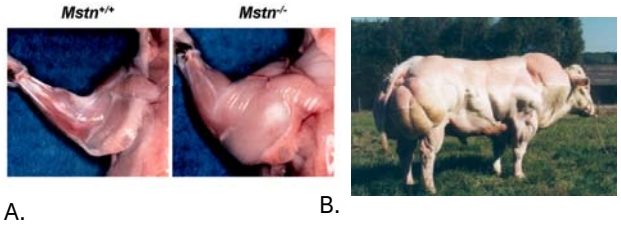

Fig. 1. Myostatin deficiency produces a dose-dependent increase in muscle mass. Mice (A) and cows (B) lacking myostatin (Mstn$^{-/-}$) show dramatic increases in muscle mass. Images from McPherron et al.[3] and McPherron and Lee.[4]

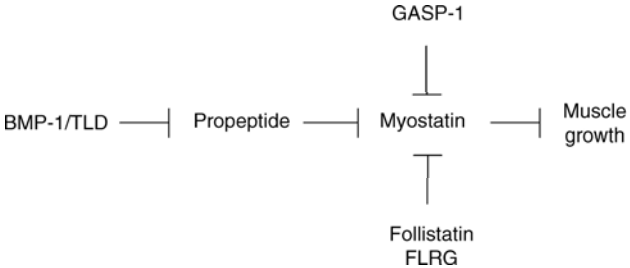

Fig. 2. Myostatin suppresses muscle growth and hypertrophy, and myostatin function can be inhibited by myostatin propeptide. Myostatin activity is inhibited by extracellular binding proteins, including its propeptide, follistatin, FLRG, and GASP-1. Reproduced from Lee (2004).[1]

METHODOLOGY:

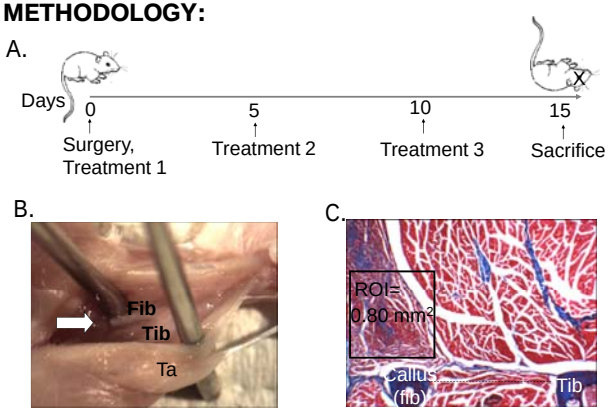

Fig. 3 Treatment intervention, surgical approach, and assessment of soft-tissue repair. (A) Surgery & treatment schedule. (B) Osteotomy site (arrow). Fib-fibula, Tib-tibia, TA-tibialis anterior. (C) Soft-tissue sections were stained using Masson trichrome and region of interest (ROI) measured for fraction of fibrotic tissue (blue).

RESULTS:

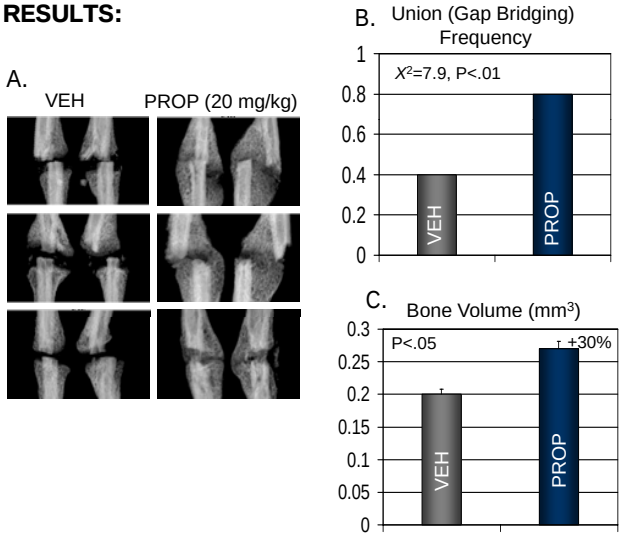

Fig. 4. Myostatin propeptide enhances bone healing. Increased bone observed in the osteotomy site of propeptide-treated (PROP) mice (A), increased frequency of osteotomy gap-bridging (B) with treatment, and greater bone volume in the callus of treated mice (C).

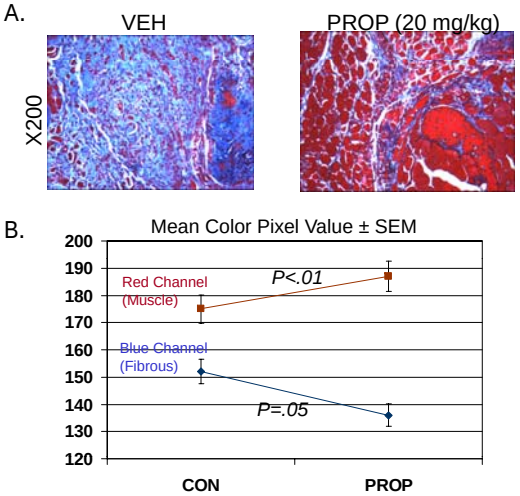

Fig. 5. Recombinant myostatin propeptide decreases fibrosis and scarring in injured muscle. Trichrome-stained sections showing greater muscle- (red) and decreased fibrotic tissue-staining (blue) in treated mice (A). Image analysis showing treatment effects (B).

CONCLUSIONS:

Blocking myostatin signaling in the injured limb improves fracture healing and enhances muscle regeneration. These data suggest that myostatin inhibitors may be effective for improving wound repair in cases of orthopaedic trauma and extremity injury.

REFERENCES:

1. S.-J. Lee (2004) *Ann Rev Cell Dev Biol* 20: 61.

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