The elusive promise of myostatin inhibition for muscular dystrophy

Kathryn R. Wagner, a,b

INTRODUCTION

Myostatin (growth differentiation factor 8, GDF8) is a Transforming Growth Factor-β (TGF-β) family member expressed predominantly in skeletal muscle [1]. It functions as a negative regulator of muscle growth. Myostatin treatment of myoblasts show decreased proliferation and differentiation [2–4]. Genetic deletion of myostatin has been associated with increasing muscle mass in mice, cattle, dogs, horses, and other species, indicating its evolutionary conservation [1,5–8]. Discovery of a hypermuscular child who was homozygous for an splice site mutation, which resulted in a premature stop codon, suggested that inhibition of myostatin might confer therapeutic benefits for muscle wasting disease in humans [9].

Preclinical inhibition of myostatin in mouse models supported clinical trials in muscular dystrophy. Approximately a dozen different successful approaches to inhibiting myostatin have been studied in animals. Common effects of these inhibitors include increased muscle mass and strength with decreased fibrosis. There appeared to be little if any toxicity to inhibiting myostatin specifically, adding to its attractiveness as a therapeutic target. However, although myostatin inhibition in clinical trials have shown little in the way of side effects, there appears to be a disconnect between preclinical and clinical efficacy in muscular dystrophy. Six randomized, double-blinded, placebo-controlled (RDBPC) trials of various myostatin inhibitors in both pediatric and adult muscular dystrophies did not lead to further development primarily because of lack of efficacy [10–14]. Currently, the future of myostatin inhibitors as a monotherapy for muscular dystrophy seems improbable.

THE PRECLINICAL PROMISE

The development of pharmacological and gene therapy-based inhibitors of myostatin have taken advantage of an understanding of its molecular signaling. Myostatin circulates as a dimer in a latent form, noncovalently bound to its own inhibitory

*Center for Genetic Muscle Disorders, Kennedy Krieger Institute and bDepartments of Neurology and Neuroscience, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Correspondence to Kathryn R. Wagner, MD, PhD, Center for Genetic Muscle Disorders, Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205, USA. Tel: +1 443 923 9525; e-mail: wagnerk@kennedykrieger.org

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prodomain. When the prodomain is proteolytically cleaved, the myostatin dimer is active and binds to a heterodimer receptor, the activin type IIB receptor (ActRIIB) and the type 1 receptor Alk4 or Alk5. This induces phosphorylation of Smad2/3, which leads to recruitment of Smad 4. The Smad heterocomplex translocates to the nucleus where it regulates transcription of target genes (reviewed in [15]; see Fig. 1).

The design of myostatin inhibitors have included neutralizing monoclonal antibodies and adnectins, modified follistatin (a natural antagonist of myostatin delivered as a recombinant protein, peptibody, fusion protein, or via adenoassociated virus, AAV), myostatin inhibitory prodomain (delivered as a peptide, peptibody, or via AAV), a soluble version of ActRIIB (delivered as a Fc fusion protein or via AAV), myostatin targeted siRNA, antisense oligonucleotides inducing myostatin exon skipping and myostatin receptor blocking antibodies (see Fig. 1). Some of these approaches, such as modified follistatin and soluble ActRIIB-Fc, bind other TGF-β family members in addition to myostatin such as activins, bone morphogenic proteins (BMPs), and other GDFs, the inhibition of which has been shown to augment the hypertrophic effects on skeletal muscle [16,17*,18,19*].

Inhibition of myostatin as a potential therapeutic for muscular dystrophy was first studied in the mdx mouse, which has a premature stop codon in the gene for dystrophin and thus is a model of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) [20]. Mdx mice lacking myostatin had increased myofiber size with increased muscle weights, improved grip strength, and decreased fibrosis compared to their mdx counterparts [21]. Studies of postnatal inhibitors of myostatin in mdx similarly demonstrated increased muscle weight and strength with decreased fibrosis [17*,22–26]. However, in none of these studies did the degree of increase in muscle strength mirror the degree of muscle hypertrophy. There have also been concerns that in many physiological studies, the absolute force of isolated muscles increased with myostatin inhibition but the specific force (force per cross sectional area) did not. The clinical relevance of specific force versus absolute force is unclear.

Myostatin inhibition has had varying success in several mouse models of other muscular dystrophies. Treatment of the γ-sarcoglycan-deficient mouse model of limb girdle muscular dystrophy (LGMD2C/LGMDR5) resulted in increased muscle mass and absolute force but no improvement in pathology or specific force [27]. Similarly, in the TIC-DUX4 mouse model of facioscapulohumeral muscular dystrophy (FSHD), AAV-follistatin gene therapy resulted in increased muscle mass and absolute force but not specific force [28**]. Recently, treatment of the A17 mouse model of oculopharyngeal muscular dystrophy (OPMD) with a neutralizing antibody to myostatin was shown to increase muscle strength and absolute force while improving pathological features including fibrosis [29*]. Another recent study from the same group in aged A17 mice showed reduction in fibrosis but minimal effect on muscle mass or other pathological features [30]. Further indication that there may be a therapeutic window for myostatin inhibition comes from a study of anti-myostatin anti-bodies in the δ-sarcoglycan mouse model of LGMD2C/LGMDR5, which reported increased muscle mass and reduce fibrosis in young but not old animals [31]. Finally, in other preclinical models of muscular dystrophies, the benefits of myostatin loss or inhibition were unclear. For example, laminin-deficient mice (a model of merosin-deficient congenital muscular dystrophy type 1A, MDC1A), which were lacking myostatin did not have improvement in pathology and had increased perinatal lethality likely a cause of loss of brown fat [32]. In the dysferlin-deficient mouse model for LGMD2R/LGMD2B, treatment of ActRIIB-Fc was associated with increased muscle mass and decreased fibrosis but with increased creatine kinase and overexpression of follistatin in this model resulted in increased muscle necrosis [33]. AAV-mediated expression of myostatin prodomain in the calpain-deficient mouse model of LGMDR1/LGMD2A was associated with increased muscle mass and absolute force in one study [34]. However, a recent report in the same animal model overexpressing follistatin or treated with neutralizing antibodies showed only increased muscle mass with no improvement in strength and further loss of oxidative capacity which is a hallmark of calpain deficiency [35*].
In addition to promoting an increase in muscle quantity, several preclinical studies suggested that myostatin inhibition or loss improves the muscle quality through enhanced regeneration and decreased fibrosis. Muscle from myostatin null animals acutely injured with toxin express myogenic regulatory factors and regenerate large-diameter myofibers earlier than controls [36,37]. Mice overexpressing follistatin regenerated more quickly from a laceration injury than controls with larger myofibers at every time point [38]. In addition to its regulation of muscle progenitor cells and myofibers, myostatin stimulates the proliferation of fibroblasts and production of extracellular matrix proteins [39,40]. Inhibition of myostatin with ActRIIB-Fc led to a reversal of preexisting fibrosis within aged mdx mice, through a process of fibroblast apoptosis [40]. These studies suggest that myostatin has a number of functions on muscle and that inhibition could lead to both increased quantity and quality of muscle.

**CLINICAL DISAPPOINTMENTS**

There have been six RDBPC trials of myostatin inhibitors in muscular dystrophy to date. These
trials studied different myostatin blocking strategies, different disease populations (three in pediatric DMD, 2 in adult MDs) different routes of administration, different trial durations, and different outcome measures. In general, these trials demonstrated safety of myostatin inhibition with some concerns raised for nonspecific myostatin inhibitors. Except for one trial (with ACE-083), there was negligible increases in muscle mass, a hallmark of myostatin inhibition. None of the trials demonstrated functional efficacy.

The first trial of a myostatin inhibitor in muscular dystrophy was initiated nearly 15 years ago by Wyeth Pharmaceuticals (now Pfizer, Inc.; NCT00104078) [14]. This was a RDBPC, dose escalation trial of a neutralizing monoclonal antibody to myostatin, stamulumab (MYO-029), delivered intravenously biweekly for 6 months to 116 patients with BMD, FSHD, and various LGMDs [41]. Stamulumab was found to be relatively safe and well tolerated with the exception of some cutaneous hypersensitivity reactions at the highest doses. Exploratory efficacy outcome measures of muscle mass and function showed no statistically significant differences between treated and controls. There were trends of increased lean body mass by DXA and increased myofiber diameter by muscle histology. The trial was underpowered to detected statistically significant differences among cohorts. In addition, subsequent pharmacokinetic and pharmacodynamics analysis of stamulumab also suggested the average stamulumab concentration needed to cause a 50% effect on monkey muscle circumference was approximately 20× higher than in mouse, suggesting a significant potency shift between the two species [42]. When compared with potency in monkey, maximum antibody concentration at the highest dose cohort in muscular dystrophy subjects only provided 50% effect, and the trough concentration at the steady state only maintained approximately 10% of the maximum effect seen in monkeys [42]. Therefore, it is likely that exposures of stamulumab in humans did not demonstrate high target coverage leading to lack of effect on muscle mass.

The first trial of a myostatin inhibitor in DMD explored safety and efficacy in a RDBPC, dose escalation trial of ACE-031 by Acceleron Pharma (NCT01099761) [12]. ACE-031 is an ActRIIB-Fc fusion protein and unlike MYO-029 is not a selective inhibitor but also blocks BMP8, BMP9, and activins [16]. Eighteen patients received ACE-031 and six patients received placebo every 2–4 weeks by subcutaneous injection for 12 weeks [43]. There were dose dependent, statistically significant changes from baseline in the lean body mass by DXA up to +4.1% in the high-dose cohort compared to +2.5% in the placebo cohort [43]. There were trends for increased 6-min walk distance (6MWD) in treated versus placebo patients [43]. However, nonselective inhibition, particularly of BMP8 and BMP9, involved in angiogenesis, is likely what contributed to unacceptable side effects of nose and gums bleeds and facial telangiectasia that led to the study being discontinued before the highest dose cohort was enrolled [43]. This trial was limited by the small sample size and unacceptable side effects of ACE-031 but likely encouraged others to continue to pursue myostatin inhibition for DMD.

A subsequent trial of a myostatin inhibitor in ambulant DMD was a RDBPC within-patient dose escalation trial of domagrozumab (PF-06252616) by Pfizer Inc. (NCT02310763) [10]. Domagrozumab is a neutralizing monoclonal antibody to myostatin whose murine equivalent, mRK35, showed significantly higher binding affinity to myostatin and increases in muscle mass compared to MYO-029 in mouse models [44]. The trial consisted of two 48-week periods during each of which the 120 patients with DMD were treated with escalating doses of weekly, intravenous, domagrozumab, or placebo [45]. The drug was found to be generally safe and well tolerated [45]. The primary efficacy endpoint, the mean change in four stair climb (4SC) time at week 49 compared to baseline showed no statistically significant difference between domagrozumab and placebo treated individuals [45]. There were no significant differences in the 4SC between historical controls and domagrozumab treated subjects at 97 weeks [45]. Although there were directional favorable differences for the thigh volume by MRI and the NSAA in domagrozumab versus placebo or historical controlled cohorts, none of the differences in secondary outcome measures were statistically significant [45]. The domagrozumab trial was a well powered study of sufficient treatment duration (up to 2 years) and the lack of efficacy signal cast doubt on the therapeutic utility of myostatin inhibition in muscular dystrophy, specifically DMD.

Other RDBPC controlled trials of a myostatin inhibitor in ambulant DMD, RG6206 (BMS-986089/Talditercept alpha)/R07239361 were initiated by F. Hoffman-La Roche AG (NCT03039686) [11]. RG6206 is an antymyostatin adnectin, which is a single-strand fusion protein containing domains of fibronectin [46]. The first trial of RG6206 in DMD enrolled 43 ambulant boys in a phase 1, 24-week, RDBPC, dose escalation trial (NCT02515669) [47]. The primary objective was safety and tolerability [48]. RG6206 was found to be generally safe and well tolerated with the exception of occasional mild injection site reactions [48]. Inhibition of free myostatin levels approached 95% in the highest dose
cohort [48]. Lean body mass index increased 3.85% in treated versus placebo cohorts and contractile cross sectional area of the thigh by MRI increased 5.49% [48]. These results encouraged a phase II/III trial RDBPC trial of two different doses of RG6206 in 166 ambulant DMD boys for 48 weeks [11]. Patients received study drug or placebo subcutaneously every week for 48 weeks [11]. The primary outcome measure was change from baseline of the NSAA [11]. The results of this phase II/III trial in RG6206 have not yet been released at the time of this writing, however Roche terminated the study after a preplanned interim futility analysis indicated that the compound was ‘highly unlikely to demonstrate clinical benefit as defined by meeting the primary endpoint’ [49].

The safety and efficacy of a nonselective myostatin inhibitor, ACE-083, was studied in a phase II trial in FSHD by Acceleron Pharma (NCT02927080) [13]. ACE-083 is a modified follistatin-Fc fusion protein that binds myostatin, GDF11, BMP6, BMP7, activin A, and activin B [19∗]. Part I of the study was an open label study of 23 patients receiving escalating doses of ACE-083 delivered by intramuscular injection into either the biceps or tibialis anterior every 3 weeks for 3 months [13]. This study showed that ACE-083 was safe and well tolerated with the exception of injection site reactions, myalgias, and one incidence of lower extremity muscle swelling [50]. Contractile muscle mass was increased by greater than 15% in the highest dose cohorts [50]. Part II of the study was a RDBPC study of the optimal dose delivered intramuscularly every 3 weeks for 6 months to 56 patients with FSHD [13]. The original primary outcome measure for part 2 was percentage change from baseline of muscle volume of injected muscle by MRI [13]. The results of this trial have not been made public but Acceleron released a press statement that indicated that the trial met its primary objective of increased muscle mass but did not meet any of its secondary outcome measures of muscle function. It therefore decided to terminate ACE-083 for FSHD [51].

These six trials suggest that specific myostatin inhibition is safe and well tolerated. Nonspecific systemic administration of myostatin inhibitor, such as seen with ACE-031, may have some side effects because of inhibition of other TGF-β family members which are often widely expressed and have multiple systemic functions. Activin and follistatin, for example have roles in inflammation, wound healing, and reproduction. Only ACE-083 was associated with a likely clinically meaningful increase in muscle mass. No trial demonstrated functional efficacy.

**WHY THE LACK OF TRANSLATION?**

Approximately 95% of drugs entering clinical trials fail to reach their primary endpoint [52]. To learn from these failures, it is important to evaluate why myostatin inhibition in muscular dystrophy has not translated from a wealth of promising preclinical studies to success in the clinic. The trials did not all fail to show efficacy for the same reasons. For example the stamulumab trial, as the first trial of a myostatin inhibitor in muscular dystrophy, was unique in investigating a weak inhibitor of myostatin in multiple small subsets of subjects with varying muscular dystrophies treated with several different doses, leading to a study underpowered for efficacy [41]. ACE-031 was a small study of only 12 weeks duration that had a suggestion of biological activity but which was terminated because of side effects of nonspecific BMP inhibition [43]. ACE-083 administration resulted in a potentially clinically meaningful increase in muscle mass, but likely because of the limitations of treating only a single muscle, did not result in increases in function which require multiple muscle groups [51]. However, domagrozumab and RG6206 cannot be so easily explained and require additional consideration.

The domagrozumab and RG6206 studies in DMD were well powered and of sufficient length to potentially demonstrate efficacy. The fact that none of the secondary functional outcome measures showed statistically significant changes from baseline suggest lack of efficacy was not because of a problem with the selection of the primary outcome measure. Both domagrozumab and RG6206 bound 95–97% of free circulating myostatin indicating excellent target engagement [45∗,48]. RG6206 produced up to ~30% increased muscle mass in SCID mouse muscles but only 5% in monkeys after 4 weekly doses [46]. RG6202 could not be tested in mdx mice because of the lack of a murine surrogate and the generation of neutralizing antibodies (M. Ahljanian, personal communication). The murine equivalent of domagrozumab, mRK35, was associated with a 23–26% increase in muscle weights and a corresponding increase in grip strength and tetanic force in mdx mice [26]. Domagrozumab led to a robust response of increased muscle mass in monkeys where muscles increased in size from 23.7 to 36.5% [26]. Finally, in healthy human individuals, just three doses of 10 mg/kg of domagrozumab led to an increase of 4.49% muscle volume by MRI (compared to DMD boys who received up to 40 mg/kg domagrozumab for several months) [53].

However, domagrozumab was not associated with a statistically significant increase in muscle volume in the DMD trial at 49 weeks [45∗].
RG6202 in the phase I trial in DMD was associated with a small, 5.4% increase in muscle volume at 24 weeks [48]. Muscle hypertrophy is a uniform biomarker of myostatin inhibition and the lack of increased muscle volume suggests that there was little to no biological effect of myostatin inhibition in DMD. Why did DMD muscle not respond to myostatin inhibition similar to mdx muscle? First, circulating myostatin is approximately 10-fold lower in humans than in mice [54]. Second, circulating myostatin protein levels and skeletal muscle myostatin RNA levels are downregulated in DMD and mdx muscle [54,55]. However myostatin levels are proportionately much more suppressed in DMD than mdx likely because of greater pathology. In the mdx, skeletal muscle myostatin is 25% of wildtype levels whereas in DMD it is 8% of healthy human controls [54,55]. These differences between species in total levels of myostatin and downregulation of myostatin expression in disease suggest that the mdx mouse may not be a good model of DMD as regards to myostatin inhibition.

The golden retriever muscular dystrophy dog model (GRMD) lacking dystrophin has a more severe phenotype than the mdx mouse and has myostatin muscle expression levels more similar to human DMD, on average 13% of normal dogs [56]. A study of the genetic loss of myostatin in the GRMD model was concerning for disproportionate muscle growth, increased joint contractures and no statistically significant changes in strength in GRMD lacking myostatin [57]. However, more encouraging results were reported in a study that treated GRMD dogs with AAV expressing a modified myostatin prodomain [58]. After 13 months post treatment cross sectional area of various hindlimb muscles had increased 18–25% by MRI although strength was not assessed [58]. In summary, the mdx mouse model likely does not replicate DMD as regards to the effects of myostatin inhibition on skeletal muscle mass and strength and the experience with larger animal models of disease such as the GRMD is at present too limited to know if it is more predictive.

Another potential reason for failure of translation is the effect of concomitant medications that participants continued while enrolled in the domagrozumab and RG6202 trials. In most mdx studies, myostatin inhibition was tested alone, whereas the standard of care for DMD includes treatment with corticosteroids and angiotensin converting enzyme inhibitors or angiotensin receptor blockers among others [59]. A recent report from Hammers et al. [60] suggested that concomitant prednisone treatment of mdx mice nullified the increased muscle mass and strength induced by a modified myostatin propeptide. This contrasts however with results with the murine surrogate of domagrozumab, mKR35, which produced similar increases in body weight and lean muscle mass in mdx mice with and without corticosteroid treatment [26]. Although the effects of corticosteroids on myostatin inhibition in the mdx mouse are unresolved, these observations underscores the need to test novel therapeutics in combination with standards of care.

The lack of efficacy of myostatin inhibitors in two large DMD trials will likely discourage future development of this therapeutic strategy as monotherapy for DMD. However, myostatin inhibition may yet be considered for adjuvant therapy along with antisense oligonucleotides (ASO) or gene therapy. Two ASOs, eteplirsen and goldlersin, have recently been approved for specific subsets of DMD and minidystrophin gene therapy is currently in clinical trials. Combining ASOs that induce exon skipping to generate dystrophin and disrupt myostatin led to synergistic effects with increased dystrophin expression compared to ASO alone in mdx mice [61]. Importantly, these results were replicated in aged mdx mice which have greater pathology and are a better model of DMD [62*]. One could also imagine myostatin inhibition being used to ‘prime’ skeletal muscle for minidystrophin gene therapy. A reduction of fat and fibrosis through pretreatment with a myostatin inhibitor could potentially increase the efficacy of AAV delivered minidystrophin gene therapy. These hypotheses will need to be tested in large animal models of DMD that more closely resemble the human disease.

Finally, although DMD may be too challenging a disease for myostatin inhibition, other muscular dystrophies may be more amenable. BMD and FSHD, for example, have higher baseline levels of myostatin expression than DMD [54,55]. The mdx mouse may more closely model BMD than DMD and may be more predictive of clinical response. There are several mouse models of FSHD and as described above, one has already shown amelioration with follistatin overexpression [28**]. Finally, ACE-083 provides proof of concept that nonspecific inhibition of myostatin in FSHD can result in significant muscle hypertrophy [50].

**CONCLUSION**

There have been dozens of studies in mouse models of muscular dystrophy, most of which support a benefit of myostatin inhibitors with some notable exceptions. However, mouse models, may not accurately reflect myostatin signaling in human disease as suggested by the mouse’s higher circulating levels of myostatin and lower downregulation of baseline...
levels in disease states. Monkeys and healthy human volunteers also exhibited increased muscle mass from treatment with various myostatin inhibitors but again, myostatin signaling in healthy muscle does not predict that in dystrophic muscle. Systemic administration of myostatin inhibitors in muscular dystrophy patients resulted in little if any increase in muscle mass. Since animal models suggest that increased muscle function as a result of myostatin inhibition is a fraction of increased muscle mass, it is not surprising that no functional benefits were observed. It is still not known what degree of increased muscle hypertrophy is required to confer increased muscle function in muscular dystrophy patients but increases on the order of 5% as seen in some of the previous clinical trials is unlikely to result in clinically meaningful benefit. It is conceivable that myostatin inhibition has a role to play in muscular dystrophies other than DMD or as adjuvant treatment of DMD along with molecular therapies such as ASO and gene therapy.

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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
+ of outstanding interest

18. This study compared a modified follistatin-Fc to ActRIIB-Fc and myostatin neutralizing antibody in the mdx mouse. At equivalent doses, modified follistatin-Fc showed less muscle hypertrophy and force production than ActRIIB-Fc and more than myostatin neutralizing antibody delineating differences in nonspecific and specific inhibitors.
20. Pearsall RS, Davies MV, Carnell M, et al. Follistatin-based ligand trap ACE-083 induces localized hypertrophy of skeletal muscle with functional improve-
21. This paper led to increased muscle size and strength when injected locally in the mdx model of DMD and the Trehal-J mouse model of CMT1A. These results encouraged the subsequent clinical trials of ACE-083 in FSHD and CMT1A.
23. This is the first preclinical study to evaluate the potential functional benefits of systemic myostatin inhibition in an animal model of FSHD. The authors developed a novel mouse model of FSHD in which DUX4 mediated disease is transducible and displays muscle pathology and weakness. AAV-V1 follistatin treatment of this model resulted in increased muscle mass and strength providing proof of concept for this therapeutic modality in DUX4 mediated disease.
Muscular disease


OPMD is a rare muscular dystrophy for which there are no clinically meaningful treatments. This is the first study to evaluate whether myostatin inhibition is a potential therapeutic option for this disease. A17 mice were treated with mRK35 resulting in increased mass and strength. It will now be important to determine to what level myostatin is downregulated in OPMD.


This was a well powered RDBPC 2-part study (48 weeks each) of a specific myostatin inhibitor in ambulatory DMD. Domagrozumab was found to have a good safety profile, good target engagement but little to no efficacy in increasing muscle mass or strength. These negative results call into question the predictive value of mdx mice.


This study of concomitant glucocorticoid and myostatin inhibition treatment in mdx mice raises a concerning question about the predictive value of mdx mice not simultaneously treated with glucocorticoids, which is the standard of care for DMD.


The aged mdx mouse may be a better model of DMD than young mice. In this model, dual dystrophin and myostatin exon splicing by ASO resulted in greater dystrophin expression than dystrophin exon splicing alone. This raises the possibility that myostatin inhibition could have a role as adjuvant therapy in DMD.