Kennedy Capital Management®

Muscling our way past the crowds

Finding the hidden gems of healthcare investing

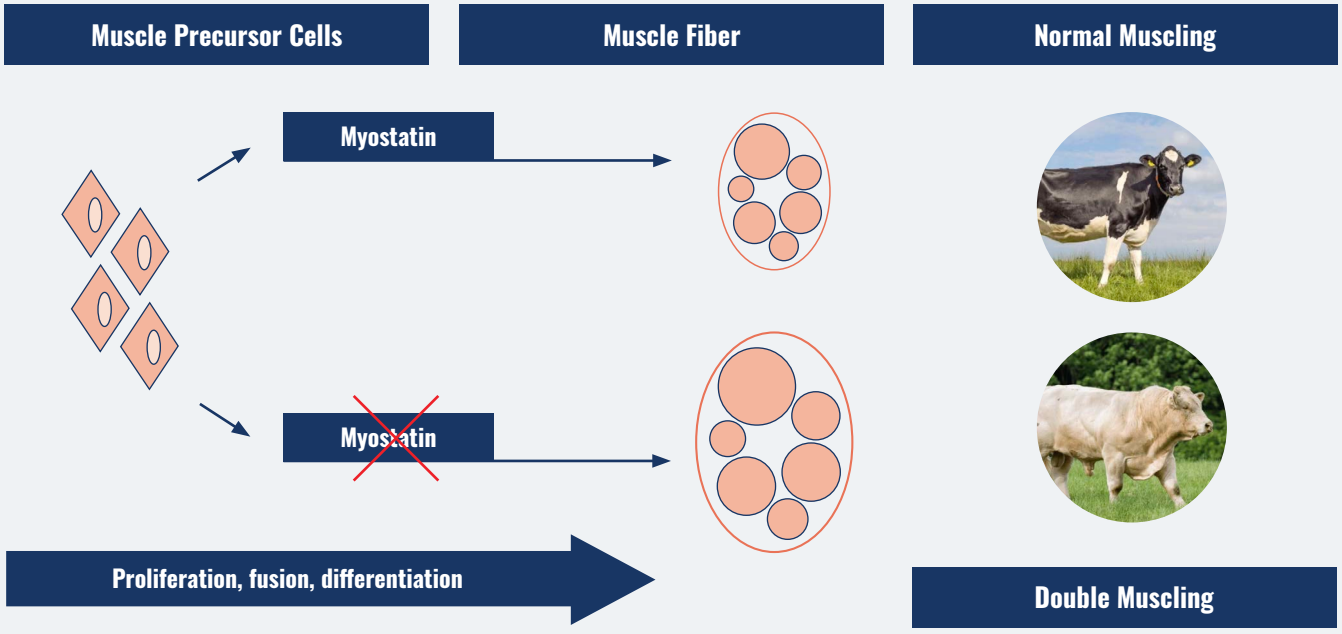
In our **last update**, we highlighted the use of GLP-1 receptor agonists in weight loss. Demand for GLP-1s continues to grow, with sales to the Type 2 diabetes and obesity markets predicted to reach more than $125 billion by 2033.

However, one of the emerging side effects of drastic weight loss using GLP-1s is muscle loss, which can account for as much as 50% of the total weight lost! This is likely due to the caloric restriction and decrease in protein intake while patients are on GLP-1s. It is by way of GLP-1s that we arrive at our topic:

Muscles, myostatin, and more!

Biceps, glutes, pecs, quads, abs—these are some of the large muscle groups with which we are most familiar. A healthy human may take their function for granted, but muscles allow us to sit up straight, walk, and regulate breathing. They also act as an important energy storage facility for the body.

Muscle cells, or myocytes, go through cycles of division just like many other cell types in the body. Unique from other types of cells, however, a single myocyte can also grow in size. Both processes are regulated by growth factors. A growth factor that's essential for controlling muscle growth is myostatin, which pumps the brakes on cell division and keeps muscle growth in check. When myostatin is impaired or non-functional, like in double-muscled cattle breeds, extreme muscling occurs due to the increased number and size of myocytes.



Muscle without going to the gym? Sign me up!

Not so fast! Inhibiting myostatin in a healthy animal has been associated with cardiac hypertrophy—an over-muscled heart. When heart muscle becomes too thick, it may not pump blood as effectively.

Further, inhibitors may impact other growth factors closely related to myostatin. This has resulted in decline in bone density and blood disorders in preclinical and discontinued clinical studies. Additionally, while complete loss of function of myostatin leads to extreme muscling and increased strength, partial loss of function due to a genetic mutation or clinically relevant dose of inhibitor may show diminishing effects in otherwise healthy people.

Finally, additional muscle fibers don't necessarily equate to increased muscle strength. Strength is related to the contractile power of each muscle fiber, which can be improved through load-bearing exercise (a.k.a. going to the gym).

To summarize:

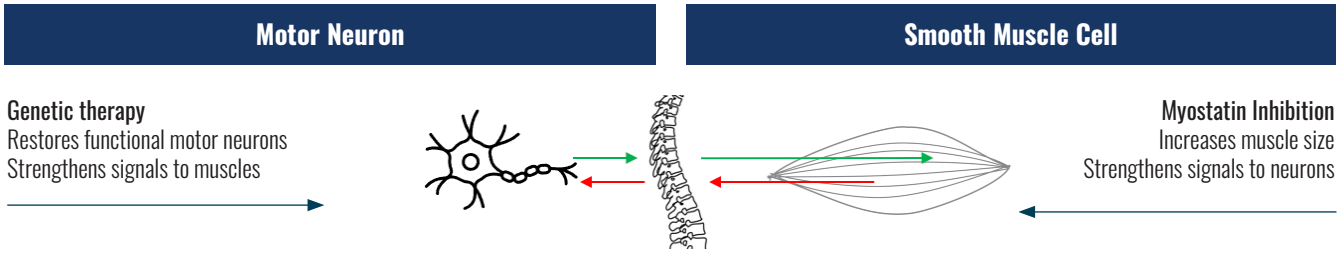
- Too much muscle can be bad for your heart.
- Myostatin inhibitors can have negative, off-target effects.
- Doses being studied in humans may not result in the over-muscling observed in cattle.
- Myostatin inhibitors don't strengthen the muscle cells you have—you'd still need to go to the gym to build strength.

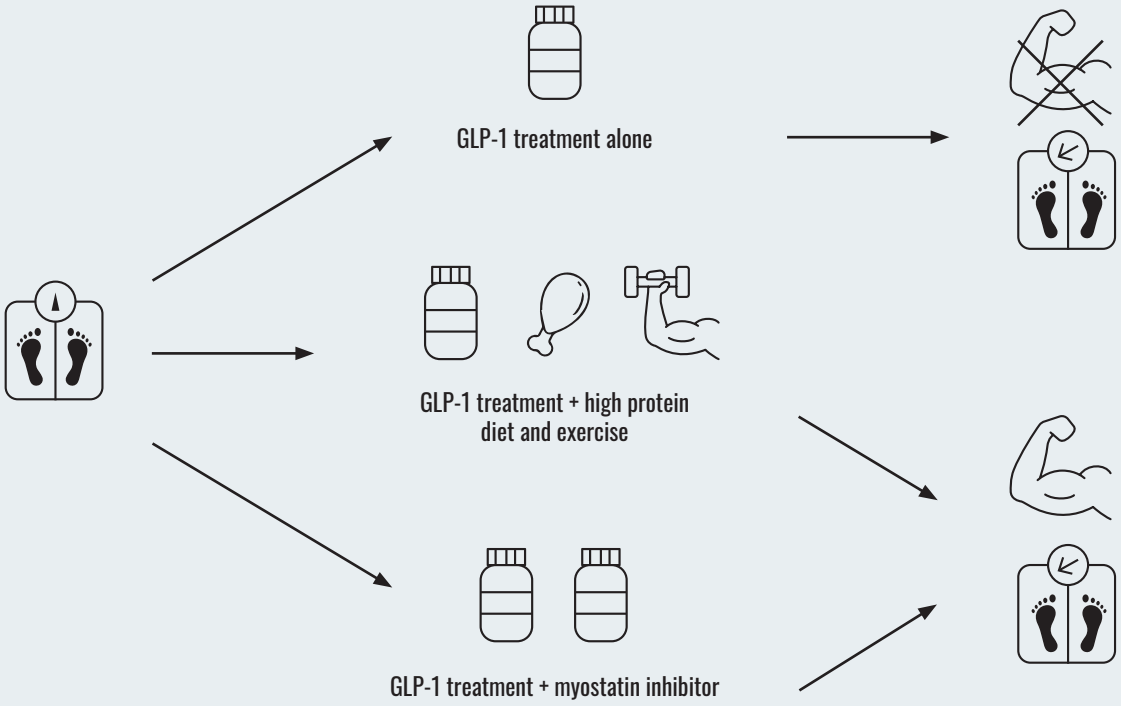
Fitness shortcuts aside, why develop these drugs in the first place?

There are several diseases in which muscle fibers are damaged or destroyed, including Duchenne Muscular Dystrophy (DMD), Facioscapulohumeral Muscular Dystrophy (FSHD), and Spinal Muscular Atrophy (SMA), to name a few.

SMA is characterized by the death of motor neurons and progressive skeletal muscle wasting and weakness. This disease is a unique case because it spurred development of several new therapies—the first oligonucleotide therapy was approved in 2016, the first gene therapy was approved in 2019, and the first siRNA therapy was approved in 2020. All of these treatments increase the production of the deficient protein that causes SMA.

Replacement of this protein helps SMA patients regain and maintain some motor function for longer, but it can still be hard to build back the muscle that was lost during years of atrophy. Myostatin inhibitors are being assessed in late-stage trials by several companies to rebuild that lost muscle in SMA patients.





Muscle wasting and obesity—an unintended side effect.

Coming full circle now—back to GLP-1s and weight loss. As mentioned earlier, as much as 50% of weight lost on GLP-1 therapy is lean muscle loss. That's likely because GLP-1s slow digestion and stimulate insulin production—decreasing appetite and reducing caloric intake.

This is an excellent mechanism for weight loss, but it also starves the body of the building blocks for muscle. It's important to preserve lean muscle mass for metabolic benefits, long-term weight management, and overall better health outcomes. Less muscle, especially in those over 65 years of age, can also result in increased risk of falls and hospitalization.

Maybe you can see where this is going. Myostatin inhibitors may be useful in preventing the muscle loss associated with GLP-1 use—enabling obese or diabetic patients to improve their weight and glycemic control without becoming frail.

An added bonus? Building muscle also contributes to fat loss by increasing energy use by skeletal muscle cells.

Preclinical data show up to 25% muscle gain and up to 20% fat loss in obese mice treated with a myostatin inhibitor. Early data in humans show up to 20.5% fat loss and 3% muscle gain in obese adults.

This fat loss and muscle gain can be difficult to interpret across Ph. 1 studies but generally point to a potential role for myostatin inhibitors in the treatment of obesity. Some studies are already advancing trials of myostatin inhibitor and GLP-1 combinations, the first data for which are expected as early as 2025.

Good thing somebody is paying attention, with so many people taking GLP-1s!

There may be more than one correct answer to this weight- and muscle-loss conundrum. Recent data from an amylin molecule—one mechanism intended to decrease appetite—showed less muscle loss than typically observed in GLP-1 studies. Another dataset from a molecule combining glucagon and GLP-1 receptor activity showed relatively less muscle wasting than a GLP-1 receptor agonist alone. A combination of many approaches may end up being the ideal solution, and we still have a lot to learn about the safety and efficacy of all options in development.

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25,000

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42%

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Our approach to myostatin inhibitor investment

We believe myostatin inhibitors can impact both rare disease and large indications, with several opportunities materializing outside of SMA and obesity. We're mindful that the obesity landscape is evolving rapidly and that myostatin inhibitors are still in the early stages of research in that patient population. Future studies will need to show clinical benefit—likely in addition to GLP-1s—to be approved for use in obesity. Studies may show the effectiveness of myostatin inhibitors in treating other conditions of muscle wasting such as additional genetic conditions, cachexia, and aging.

With more than 25,000 people starting Wegovy each week and 42% of the adult U.S. population being obese, the opportunity for myostatin inhibition in combination with weight loss medications is growing. In patients over 50, age-related muscle loss has already begun in 10% of patients. Past this age, adults typically lose muscle mass each year. Combining a weight loss agent with an existing case of age-related muscle loss may spell worse outcomes and quality of life for these older patients who make up 45% of the treatable population, or roughly 50 million people.

While some large pharma players are developing myostatin inhibitors expressly for use in combination with weight-loss offerings, we believe greater opportunities may exist in the handful of small cap companies developing myostatin inhibitors indications in addition to obesity, like the rare neuromuscular disease SMA.

These smaller indications confer several advantages, including:

- Expedited FDA review if data are positive
- Rare disease price dynamics
- Seven-year market exclusivity thanks to Orphan Drug Designation, also assigned by the FDA to treatments that address rare and high unmet need indications

The rare muscular dystrophy market is smaller than obesity (in the U.S., estimated at 250,000 people versus 105 million, respectively). Although this may be viewed as a disadvantage, it potentially enables small companies to launch drugs independently and thus realize the full return on investment versus needing to partner with a larger company in exchange for a percentage of sales.

Within muscular dystrophies, a disease-modifying therapy might expect 40% market share or more, whereas an obesity candidate competes against 20 other drugs and may capture just 5% of the market. Further, once a drug candidate has positive data in a rare disease, a larger company may feel the asset is sufficiently de-risked to allow for a commercialization partnership in a large indication like obesity.

Among small cap companies developing myostatin inhibitors, their approaches differ in several ways:

- The specificity of their molecule to mature myostatin over a latent precursor or other growth factors
- The resulting tolerability profile
- The associated change in muscle mass and strength

Their approaches may also differ in route of administration (i.e., injectable or infused) and frequency of dosing (i.e., weekly or quarterly). We believe safety will be paramount, as these inhibitors are intended for chronic use in a broad population that can be afflicted with comorbidities. The balance of safety and efficacy, as well as convenience of dosing, will determine which company takes the most share in rare disease and larger markets.

At Kennedy Capital, we approach myostatin inhibitor investment by identifying and investing in:

1

Differentiated assets: We use scientific literature and company publications to compare various inhibitors that differ in their activity profiles. This allows us to target those that may be differentiated in safety or efficacy.

2

Potential acquisition targets: Through our small-cap focus, we seek to evaluate and invest in the next generation of myostatin inhibitor assets—potential acquisition targets for large pharmaceutical companies.

3

Logical development pipelines: We assess all the assets in a company's pipeline to understand where synergies may be realized, with the goal of maximizing return on investment.

In conclusion, as we contemplate the number and strength of our muscle fibers during gym sessions, we remain optimistic about near-term data points and long-term indication expansion opportunities for this treatment modality.

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