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Mimicking the Massively Muscular

New drugs that mimic mutations found in buff animals could treat muscle-wasting diseases.

By Emily Singer

Scattered throughout the mammalian menagerie are a few supermuscular freaks: double-muscled cows more ripped than any bodybuilder; racing dogs too burly to run; sheep praised for their massively muscled buttocks; and even one small German boy, born in 2000 with muscles twice the size of those of a normal newborn. All these Herculean creatures share one thing: naturally occurring mutations in a gene that produces myostatin, a protein that blocks growth of skeletal muscle. Disable that gene, and viola--spectacular muscle growth results.

Over the past few years, pharmaceutical companies have been racing to develop ways to mimic myostatin gene mutations in the hope of treating everything from the muscle loss that accompanies muscular dystrophy, cancer, and aging to obesity and other metabolic disorders. Pharmaceutical giants [Wyeth](https://www.technologyreview.com/emily.singer/Mv%20Documents/Wyeth) (<https://www.technologyreview.com/emily.singer/Mv%20Documents/Wyeth>) and [Amgen](http://wwwext.amgen.com/index.jsp) (<http://wwwext.amgen.com/index.jsp>) are expected to release clinical-trial results of myostatin inhibitors for muscle-wasting diseases within the next few months. A smaller company, [Acceleron Pharma](http://www.acceleronpharma.com/content/company/index.jsp) (<http://www.acceleronpharma.com/content/company/index.jsp>), based in Cambridge, MA, says that its more broadly acting drug could bring more brawn than can drugs targeting myostatin alone.

"There's been a huge amount of interest for human therapeutics," says [Se-Jin Lee](http://www.mbg.jhmi.edu/FacultyDetails.asp?PersonID=371) (<http://www.mbg.jhmi.edu/FacultyDetails.asp?PersonID=371>), a biologist at Johns Hopkins University, in Baltimore. "If you could increase or maintain muscle strength as people age, you could have a tremendous impact on health and well-being."

Lee discovered more than a decade ago that mice lacking myostatin grew muscles twice the size of those of their normal counterparts. But because mice have levels of myostatin 50 to 80 times that of humans, some scientists have doubted how well the results will translate to humans. New findings published in August in the journal [PLoS ONE](http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000789) (<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000789>) suggest that other molecules are also at work in muscle. Lee found that he could double the extra growth in mice lacking myostatin--effectively quadrupling muscle mass--by turning up levels of another protein. "That means there must be other regulators that have at least as important a function as myostatin in blocking muscle growth," says Lee.





Mighty muscles: *The image shows the difference between normal mice (left) and mice that lack myostatin and overproduce another protein, giving them four times as much muscle. Scientists are developing drugs that act through similar mechanisms to treat muscle-wasting diseases.*

Credit: Se-Jin Lee, Johns Hopkins University School of Medicine

Acceleron's approach attempts to take advantage of that. Rather than designing an antibody to myostatin itself, as is being tested in the Wyeth trials, scientists at Acceleron fused a portion of the receptor molecule that usually binds to myostatin with a tag that allows the drug ACE-031 to roam freely throughout the body so that it can sop up myostatin before it activates the signal to stop muscle growth. Animal studies show that this approach boosts muscle growth more effectively than does merely eliminating myostatin, suggesting that the fusion molecule also binds to other agents that impact muscle development.

Normal mice given the drug show a 30 to 60 percent increase in muscle mass, and mice with a version of muscular dystrophy show increased grip strength, a standard measure of rodent strength. Preliminary results from primate studies show that the animals on the drug bulk up at similar rates to those seen in rodents. "Before I became involved with Acceleron, if someone had told me you could increase muscle mass by up to 60 percent in a month, I never would have believed it," says CEO John Knopf.

While it's not yet clear if similar rates will be seen in humans, high doses of anabolic steroids, which carry serious side effects, increase muscle mass by a maximum of 15 to 20 percent. And because myostatin is found only in muscle, knocking it out does not appear to have the adverse effects of broader-acting steroids.

Acceleron plans to begin trials of its drug for muscular dystrophy, a genetic disorder of progressive muscle loss that usually kills sufferers before they reach age 30, in early 2008. Trials for cancer and ALS will follow.

Acceleron's Big Pharma competitors are farther along. In 2005, Wyeth, headquartered in Madison, NJ, began a clinical trial of an antibody to myostatin that binds to it and blocks its activity, as a treatment for two forms of muscular dystrophy. Results were expected to be released late last year, but the company declined to comment on the current status. Amgen, headquartered in Thousand Oaks, CA, is analyzing results from a recently completed safety trial of its own myostatin inhibitor. The company is also testing a second inhibitor as a countermeasure to space-flight-induced muscle changes. Mice aboard the Space Shuttle *Endeavor* in August were given Amgen's experimental drug to determine if it could slow muscle

loss in microgravity.

While initial clinical trials are focused on relatively rare conditions such as muscular dystrophy, safe muscle-building drugs have a broad potential market. "There is no effective agent to prevent the accelerated loss of muscle associated with disease, infection, or illness, such as cancer, heart failure, and kidney disease and dialysis," says [William Evans](http://centeronaging.uams.edu/faculty/detail.asp?offset=10&ID=62) (<http://centeronaging.uams.edu/faculty/detail.asp?offset=10&ID=62>), director of the Nutrition, Metabolism, and Exercise Laboratory at the University of Arkansas for Medical Sciences. Muscle loss is linked to increased mortality in these patients, as well as to an individual's level of disability resulting from normal aging. "As treatments of disease like cancer and heart failure become more effective, the issue becomes more prominent," says Evans. For example, treating cancer patients with a muscle-building drug may allow oncologists to administer extra rounds of chemotherapy.

In addition to treating muscle wasting, such drugs might prove effective in treating metabolic disorders, such as insulin resistance, which is linked to obesity and diabetes. Previous research has shown that diet-induced obese mice given Acceleron's drug showed an increase in lean muscle mass and reduced fasting glucose and insulin levels. Says Evans, "I think these drugs, perhaps used in combo with exercise, might have great potential in reversing the trend toward increasing obesity and decreasing muscle mass."

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