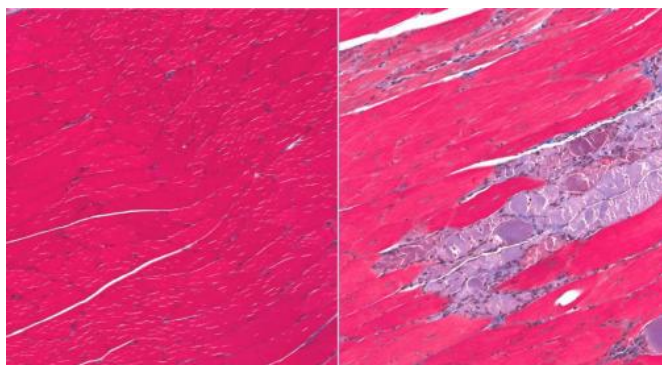


Researchers discover a key to making new muscles

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Normal muscle (left) and muscle from Muscular Dystrophy (right). Credit: Pathology

Researchers at Sanford-Burnham Medical Research Institute (Sanford-Burnham) have developed a novel technique to promote tissue repair in damaged muscles. The technique also creates a sustainable pool of muscle stem cells needed to support multiple rounds of muscle repair. The study, published September 7 in *Nature Medicine*, provides promise for a new therapeutic approach to treating the millions of people suffering from muscle diseases, including those with muscular dystrophies and muscle wasting associated with cancer and aging.

There are two important processes that need to happen to maintain [skeletal-muscle](#) health. First, when muscle is damaged by injury or degenerative disease such as muscular dystrophy, [muscle stem cells](#)—or satellite cells—need to differentiate into mature muscle cells to repair injured muscles. Second, the pool of satellite cells needs to be replenished so there is a supply to repair muscle in case of future injuries. In the case of muscular dystrophy, the chronic cycles of [muscle regeneration](#) and degeneration that involve satellite-cell activation exhaust the muscle stem-cell pool to the point of no return.

"Our study found that by introducing an inhibitor of the STAT3 protein in repeated cycles, we could alternately replenish the pool of satellite cells and promote their differentiation into muscle fibers," said Alessandra Sacco, Ph.D., assistant professor in the Development, Aging, and Regeneration Program at Sanford-Burnham. "Our results are important because the process works in mice and in human muscle cells."

"Our next step is to see how long we can extend the cycling pattern, and test some of the STAT3 inhibitors currently in clinical trials for other indications such as cancer, as this could accelerate testing in humans," added Sacco.

"These findings are very encouraging. Currently, there is no cure to stop or reverse any form of muscle-wasting disorders—only medication and therapy that can slow the process," said Vittorio Sartorelli, M.D., chief of the Laboratory of Muscle Stem Cells and Gene Regulation and deputy scientific director at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). "A treatment approach consisting of cyclic bursts of STAT3 inhibitors could potentially restore [muscle mass](#) and function in patients, and this would be a very significant breakthrough."

Revealing the mechanism of STAT3

STAT3 (signal transducer and activator of transcription 3) is a protein that activates the transcription of genes in response to IL-6, a signaling protein released by cells in response to injury and inflammation. Prior to the study, scientists knew that STAT3 played a complex role in skeletal muscle, promoting tissue repair in some instances and hindering it in others. But the precise mechanism of how STAT3 worked was a mystery.

The research team first used normally aged mice and mice models of a form of [muscular dystrophy](#) that resembles the human disease to see what

would happen if they were given a drug to inhibit STAT3. They found that the inhibitor initially promoted satellite-cell replication, followed by differentiation of the [satellite cells](#) into muscle fibers. When they injected the STAT3 inhibitor every seven days for 28 days, they found an overall improvement in skeletal-[muscle repair](#), and an increase in the size of [muscle fibers](#).

"We were pleased to find that we achieved similar results when we performed the experiments in human muscle cells," said Sacco. "We have discovered that by timing the inhibition of STAT3—like an "on/off" light switch—we can transiently expand the satellite-cell population followed by their differentiation into mature [muscle cells](#)."

More information: STAT3 signaling controls satellite cell expansion and skeletal muscle repair, *Nature Medicine*, DOI: 10/1038/nm.3656

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