Helping wasting muscles build back better

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Examples of MAGENTA prototypes fabricated with a “shape memory alloy” spring and an elastomer, and how their sizes compare to that of a one cent coin. Credit: Wyss Institute at Harvard University

Muscles waste as a result of not being exercised enough, as happens quickly with a broken limb that has been immobilized in a cast, and more slowly in people reaching an advanced age. Muscle atrophy, how clinicians refer to the phenomenon, is also a debilitating symptom in patients suffering from neurological disorders, such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), and can be a systemic response to various other diseases, including cancer and diabetes.

Mechanotherapy, a form of therapy given by manual or mechanical means, is thought to have broad potential for tissue repair. The best-known example is massage, which applies compressive stimulation to muscles for their relaxation. However, it has been much less clear whether stretching and contracting muscles by external means can also be a treatment.

So far, two major challenges have prevented such studies: limited mechanical systems capable of evenly generating stretching and contraction forces along the length of muscles, and inefficient delivery of these mechanical stimuli to the surface and into the deeper layers of muscle tissue.

Now, bioengineers at the Wyss Institute for Biologically Inspired Engineering at Harvard University and the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS) have developed a mechanically active adhesive named MAGENTA, which functions as a soft robotic device and solves this two-fold problem. In an animal model, MAGENTA successfully prevented and supported the recovery from muscle atrophy. The team's findings are published in *Nature Materials*.

"With MAGENTA, we developed a new integrated multi-component system for the mechanostimulation of muscle that can be directly placed on muscle tissue to trigger key molecular pathways for growth," said senior author and Wyss Founding Core Faculty member David Mooney, Ph.D.

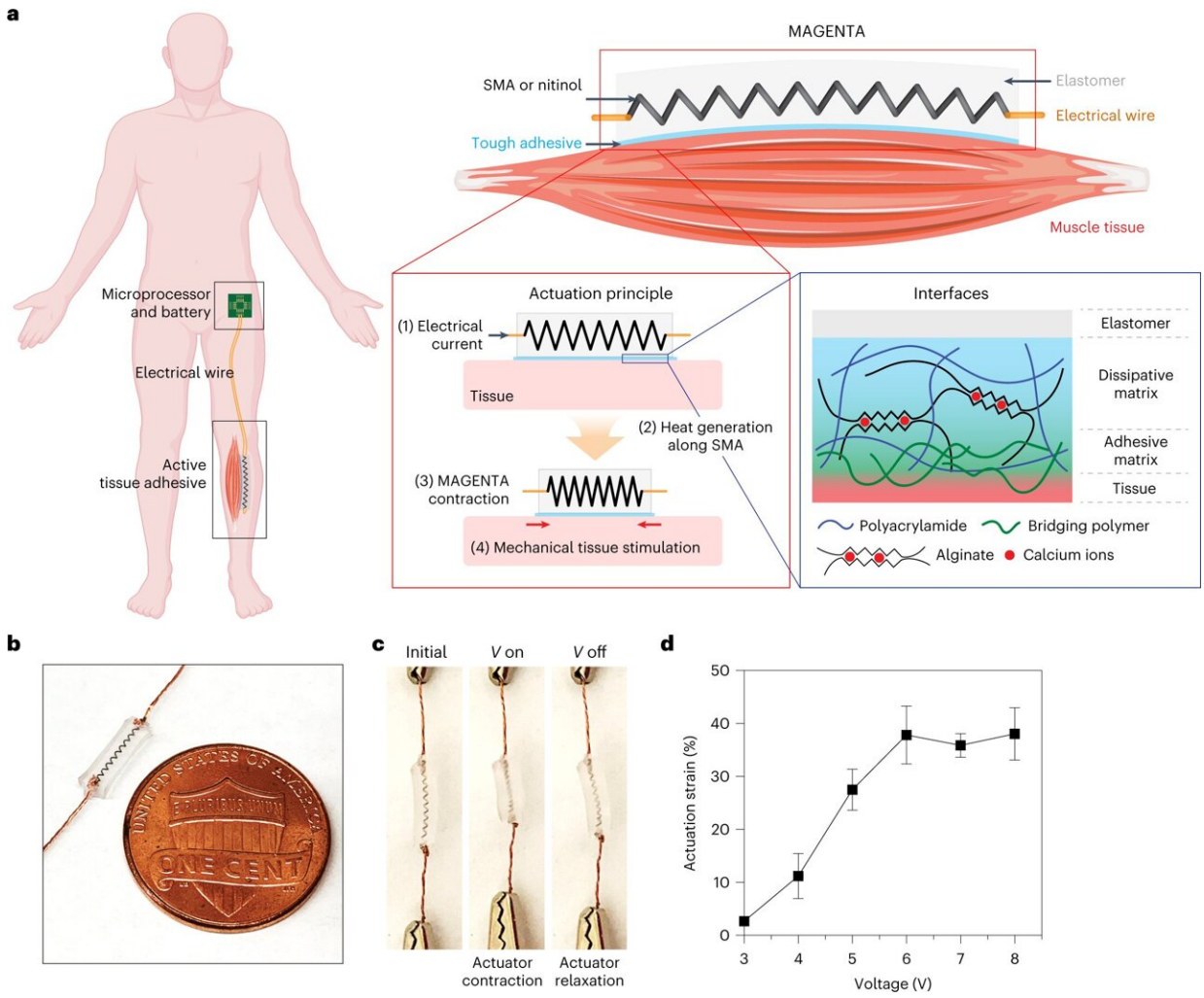
"While the study provides first proof-of-concept that externally provided stretching and contraction movements can prevent atrophy in an animal model, we think that the device's core design can be broadly adapted to various disease settings where atrophy is a major issue." Mooney leads the Wyss Institute's Immuno-Materials Platform, and is also the Robert P. Pinkas Family Professor of Bioengineering at SEAS.

An adhesive that can make muscles move

One of MAGENTA's major components is an engineered spring made from nitinol, a type of metal known as "shape memory alloy" (SMA) that enables MAGENTA's rapid actuation when heated to a certain temperature. The researchers actuated the spring by electrically wiring it to a microprocessor unit that allows the frequency and duration of the stretching and contraction cycles to be programmed.

The other components of MAGENTA are an elastomer matrix that forms the body of the device and insulates the heated SMA, and a "tough adhesive" that enables the device to be firmly adhered to muscle tissue. In this way, the device is aligned with the natural axis of muscle movement, transmitting the mechanical force generated by SMA deep into the muscle.

Mooney's group is advancing MAGENTA, which stands for "mechanically active gel-elastomer-nitinol tissue adhesive," as one of several Tough Gel Adhesives with functionalities tailored to various regenerative applications across multiple tissues.



MAGENTA provides mechanical stimulation to the target tissue. Credit: *Nature Materials* (2022). DOI: 10.1038/s41563-022-01396-x

After designing and assembling the MAGENTA device, the team tested its muscle deforming potential, first in isolated muscles ex vivo and then by implanting it on one of the major calf muscles of mice. The device did not induce any serious signs of tissue inflammation and damage, and exhibited a mechanical strain of about 15% on muscles, which matches their natural deformation during exercise.

Next, to evaluate its therapeutic efficacy, the researchers used an in vivo model of muscle atrophy by immobilizing a mouse's hind limb in a tiny cast-like enclosure for up to two weeks after implanting the MAGENTA device on it. "While untreated muscles and muscles treated with the device but not stimulated significantly wasted away during this period, the actively stimulated muscles showed reduced muscle wasting," said first-author and Wyss Technology Development Fellow Sungmin Nam, Ph.D.

"Our approach could also promote the recovery of muscle mass that already had been lost over a three-week period of immobilization, and induce the activation of the major biochemical mechanotransduction pathways known to elicit protein synthesis and muscle growth."

Facets of mechanotherapy

In a previous study published in *Science Translational Medicine*, Mooney's group in collaboration with Wyss Associate Faculty member Conor Walsh's group found that regulated cyclical compression (as opposed to stretching and contraction) of acutely injured muscles, using a different soft robotic device, reduced inflammation and enabled the repair of muscle fibers in acutely injured muscle.

In their new study, Mooney's team asked whether those compressive forces could also protect from muscle atrophy. However, when they directly compared muscle compression via the previous device to muscle stretching and contraction via the MAGENTA device, only the latter had clear therapeutic effects in the mouse atrophy model. "There is a good chance that distinct soft robotic approaches with their unique effects on muscle tissue could open up disease or injury-specific mechano-therapeutic avenues," said Mooney.

To further expand the possibilities of MAGENTA, the team explored

whether the SMA spring could also be actuated by laser light, which had not been shown before and would make the approach essentially wireless, broadening its therapeutic usefulness. Indeed, they demonstrated that an implanted MAGENTA device without any electric wires could function as a light-responsive actuator and deform muscle tissue when irradiated with laser light through the overlying skin layer.

While laser actuation did not achieve the same frequencies as electrical actuation, and especially fat tissue seemed to absorb some laser light, the researchers think that the demonstrated light sensitivity and performance of the device could be further improved.

"The general capabilities of MAGENTA and fact that its assembly can be easily scaled from millimeters to several centimeters could make it interesting as a central piece of future mechanotherapy not only to treat atrophy, but perhaps also to accelerate regeneration in the skin, heart, and other places that might benefit from this form of mechanotransduction," said Nam.

"The growing realization that mechanotherapies can address critical unmet needs in regenerative medicine in ways that drug-based therapies simply cannot, has stimulated a new area of research that connects robotic innovations with human physiology down to the level of the molecular pathways that are transducing different mechanical stimuli," said Wyss Founding Director Donald Ingber, M.D., Ph.D.

"This study by Dave Mooney and his group is a very elegant and forward-looking example of how this type of mechanotherapy could be used clinically in the future." Ingber is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children's Hospital, and the Hansjörg Wyss Professor of Bioinspired Engineering at SEAS.

More information: Sungmin Nam et al, Active tissue adhesive activates mechanosensors and prevents muscle atrophy, *Nature Materials* (2022). DOI: 10.1038/s41563-022-01396-x

Bo Ri Seo et al, Skeletal muscle regeneration with robotic actuation–mediated clearance of neutrophils, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abe8868