substitutions will lead to methods that are truly general.

Possible 'dream processes' would include the selective substitution of a carbon atom by a nitrogen atom in fully carbon-containing rings, regardless of the groups attached to the ring – thereby providing direct access to nitrogen-containing rings known as pyridines and piperidines, often found in biologically active molecules. Although some exciting examples of such substitution reactions have been reported[6,8], they work only for rings that have been chemically activated by the attachment of groups at particular positions. A general approach for the reverse nitrogen-to-carbon substitution would also be desirable, because available methods are currently limited in scope[7]. Finally, universal substitution methods involving atoms such as oxygen or sulfur would provide access to other classes of medicinally relevant compounds.

The development of such methods would keep pushing the boundaries of organic chemistry, unveiling chemical steps that could form the basis of future substitution processes. With contributions from across the community of synthetic research chemists, the swapping of atoms, at will, in the core skeletons of pharmaceutically relevant molecules might become a reality.

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Biomedical engineering

Gel implant heals muscles with electrical stimulation

Milica Radisic

An electrically conductive hydrogel injected into an injured muscle can help the muscle to regenerate and reconnect with the nervous system. This effective soft prosthesis has enabled rats to walk soon after muscular injury. **See p.58**

When a muscle is injured, its electrical communication with the nervous system is disrupted, preventing it from functioning properly. Rigid prostheses can be used to help injured people move, but these devices don't actually restore the connections that enable conscious muscle contraction. An effective prosthesis needs to conduct electrical signals in two directions – towards the muscle to stimulate it, and away from the muscle to provide feedback about how the rehabilitation is progressing[1,2]. On page 58, Jin *et al.*[3] report a soft prosthesis made from an electrically conductive material that can be injected directly into the injured muscle to help it restore this electrical circuit.

There are specific design criteria for prostheses that are injected into the body. These devices must be constructed from biocompatible materials to prevent cell death and tissue damage. They should be soft to avoid tissue injury, yet mechanically durable. And, ideally, they should be biodegradable, so that they don't need to be removed surgically after the injured tissue has regenerated.

Prostheses for electrically active tissues have even more specific requirements. They need to conduct electrical signals over long periods with high sensitivity, and their ability to activate the immune system should be limited, because this can lead to tissue engulfing the implanted prosthesis and blocking electrical signals. The tissue-interfacing prostheses developed so far do not satisfy all of these criteria – in fact, most can't be injected easily into tight spaces[2,4,5].

Jin *et al.* came up with a clever design for a soft prosthesis made from a hydrogel, a swollen polymer network containing a large amount of water. Hydrogels can flow, which makes them easy to inject and enables them to mould to a space and fill it completely. Yet hydrogels have low electrical conductivity. They are also relatively weak, which can be a problem when they are used for long periods.

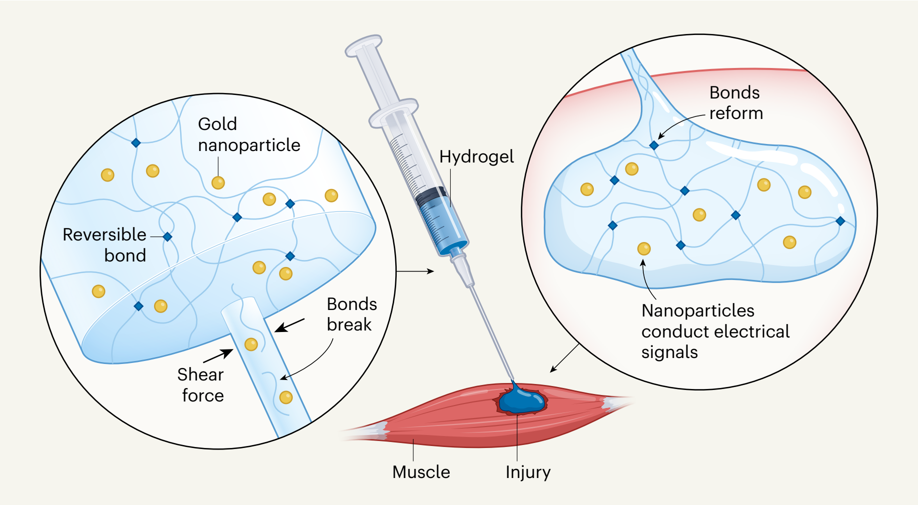

Figure 1 | An electrically conductive hydrogel prosthesis. Jin *et al.*[3] designed a soft hydrogel prosthesis to fill a defect in an injured muscle and repair its electrical connection to the nervous system. A hydrogel is a water-absorbing polymer network that can flow, but has low electrical conductivity and is relatively weak. The authors introduced gold nanoparticles to increase the hydrogel's conductivity and reversible bonds to improve its strength. The reversible bonds break under shear force, which makes the gel injectable, but they reform after the hydrogel sets in the wound.

To overcome these limitations, the authors combined their hydrogel with other materials, each of which conferred a different benefit (Fig. 1).

The polymer backbone of the hydrogel was made up of hyaluronic acid, a naturally occurring polysaccharide that has mechanical properties similar to those of soft tissues. Hyaluronic acid is known to promote tissue regeneration[6] – it is abundant during fetal development[7] – and it is useful because other molecules can be attached to the chemical groups on its backbone[8]. Yet, hyaluronic acid is not conductive, so Jin *et al.* covalently linked it to compounds containing hexagonal rings with electron clouds that can hold gold nanoparticles. Gold is a conductive, tissue-friendly and inherently inert material.

The structural weakness of hydrogels is especially problematic when they are applied to tissues that undergo repeated strain, such as skeletal muscle. Simply introducing more irreversible covalent bonds to the hyaluronic acid backbone does not help, because this makes the hydrogel too stiff to flow. Instead, the authors introduced reversible bonds, such as those supplied by the hexagonal rings[9], or by hydrogen and ionic interactions, which break under the 'shear' force produced when the gel is pushed through a needle. This allows the gel to be injected easily, but also means that the bonds can be quickly re-established after the hydrogel sets in the wounded muscle, enabling long-term stability.

Owing to this innovative chemistry, Jin *et al.* were able to support the regeneration of an injured skeletal muscle in a rat's back leg by injecting their hydrogel prosthesis, which degraded almost completely in four weeks. Importantly, the prosthesis did not cause overactivation of the rat's immune system, or the formation of scar-like fibrous tissue.

The authors also showed that their hydrogel could adhere stably to the peripheral nerve in the rat's back leg and that it could interface with conventional electric wires. This enabled the researchers to use the hydrogel to record sensory neural signals that resulted from brushing or tapping the rat's foot. And this connection worked in reverse. Jin *et al.* could activate the muscle by applying electrical stimulation through the hydrogel while it was wrapped around the nerve. Although conventional electrodes damaged the nerve after prolonged stimulation, applying the same voltage through the hydrogel did not.

Finally, the team brought all these advances together, by applying the hydrogel both around the nerve and around the muscle and connecting it to a robotic system, which supports rehabilitation of animals shortly after injury, while the rats were awake. The robot was programmed to lift the animal's foot when the electrical signal from the muscle reached a certain threshold. The system then triggered feedback stimulation through the nerve; this could be adjusted depending on the magnitude of the electrical signal coming from the muscle.

Without such nerve stimulation, Jin and colleagues found that injured animals' muscles could not produce signals strong enough to activate the robot. However, with nerve electrical stimulation through the hydrogel, the muscle signals were robust enough to engage the robotic assistance, allowing the animals to walk soon after injury.

The authors also showed that the hydrogel's ability to enable the transmission of electrical signals by increasing the conductivity around the injury was crucial. A control group without the conductive hydrogel was not able to activate the robot, owing to the absence of electrical signal transmission. Simply increasing the stimulation voltage is not a viable option because this can lead to nerve damage.

This is an impressive demonstration of an injectable conductive hydrogel as a soft tissue prosthesis, but its applicability to humans is yet to be tested. Rats' injuries are smaller than those of humans. Further studies are needed in large animals to determine whether the hydrogel can conduct efficiently over longer distances[10]. Such studies would also better qualify the regenerative potential of Jin and colleagues' hydrogel and the immune response it invokes.

The timescales for muscle regeneration in people might also be longer than those in rats, necessitating further optimization of the rate at which the hydrogel degrades. Ultimately, regulatory approval will be required for this therapy to reach humans, and it might be difficult to obtain for such a complex prosthesis. Nonetheless, Jin and colleagues' work provides a potential strategy for the development of injectable prostheses that can rapidly restore injured muscle function both by electrical stimulation and by triggering tissue regeneration.

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Structural biology

An ion transporter with features of a channel

John Orlowski

A membrane-transport protein in sperm exchanges sodium and hydrogen ions. Its activations by voltage and by cyclic nucleotide molecules are usually only features of ion channels. Structural data shed light on this protein. **See p.193 & 202**

Sperm are highly responsive to the pH level of their external and internal environments. Writing in *Nature*, Yeo *et al.*[1] (page 193) and Kalienkova *et al.*[2] (page 202) describe unusual structural features of a sperm-specific transport protein for pH regulation called SLC9C1, which exchanges extracellular sodium ions (Na^+) for intracellular hydrogen ions (H^+). The protein also has regulatory sensors, typically associated with ion channels, that are controlled by voltage across the cell membrane and by molecules called cyclic nucleotides. These characteristics make SLC9C1 well suited to regulating the intracellular pH (pH_i) of sperm, along with their motility and ultimately, fertility.

When sperm are released from the testes, they undergo an intricate, pH-dependent maturation process as they 'awaken' from a dormant state. After release, they accumulate in the adjoining epididymis tube, which contains acidic fluid (at a pH of between around 6.5 and 6.8) that renders the sperm relatively immobile. However, when sperm become a component of semen and encounter fluids in the uterus and oviducts of the female reproductive system, they enter an alkaline environment that is enriched in bicarbonate ions (HCO_3^-) and