

Better, stronger, faster

In the 1970s, the idea of building a bionic man was merely fantastical. Now we have bionic eyes and limbs, and chemists are creating artificial bodily tissues to rival nature's own, as Jon Evans discovers

In playgrounds around the world during the 1970s, children could be seen running in pretend slow-motion while making a 'na-na-na' noise. This was all due to a US television programme called *The six million dollar man*, which detailed the adventures of a former astronaut called Steve Austin (played by Lee Majors).

Austin had been seriously injured in a plane crash and then 'rebuilt' in the eponymous, rather expensive operation. This replaced his right arm and both legs and his left eye with bionic implants that gave him enhanced strength, speed and vision, and he subsequently became a secret agent. In the programme, whenever Austin employed his super speed or strength, he was shown in slow motion accompanied by an electronic grinding sound, hence the playground imitation.

Although the idea of building a bionic man was quite clearly fantastical in the 1970s, it is increasingly becoming a realistic possibility. This was showcased last year at the Experimental Biology 2006 meeting in San Francisco, US, which included a symposium entitled 'The \$6 billion (hu)man'.

Besides highlighting a quite shocking rate of inflation, this symposium also demonstrated the advanced state of much of the current work on bionic implants. For instance, William Craelius from Rutgers University, US, unveiled

the Dextra bionic hand system, which uses a patient's existing nerve pathways to control individual computer-driven mechanical fingers. Meanwhile, Daniel Palanker from Stanford University, US, presented his recently designed bionic eye. This consists of a wallet-sized computer processor, a solar battery and a small light-sensing chip implanted in the eye, and a tiny video camera mounted on virtual-reality style infrared goggles. Since then news of a US woman fitted with the world's first bionic arm has been widely reported. The arm was developed by a medical team from the Rehabilitation Institute of Chicago, US. And in February this year, researchers from the University of Southern California, US, unveiled plans for a human trial of a bionic eye which is surgically implanted into the retina.

All the bionic technologies presented at the symposium and reported in the press are electronic or mechanical devices designed to replace bodily limbs and organs. They are therefore realistic versions of the bionic implants given to Steve Austin, although they tend to be fairly bulky and most of them aren't designed to provide enhanced speed, strength or vision.

But these kinds of devices are now not the sole option available for 'rebuilding' a person, because chemists and biochemists have also been busy developing artificial

In short

- **Electronic and mechanical limb and organ replacements are already being tested on humans**
- **Chemists and biochemists are developing artificial versions of bodily organs and tissues**
- **US chemists have developed artificial collagen which improves on natural fibre**
- **Carbon nanotubes make a promising artificial scaffold on which to build stronger bones**

Chemists are helping to reignite the dream of creating a bionic man

versions of bodily organs and tissues.

This work has evolved out of efforts to fix damaged organs and tissues by stimulating cell growth within patients. For instance, a number of research groups have developed ways to incorporate bodily cells inside some kind of scaffold, such as a polymer hydrogel. The idea is that, once implanted inside a patient, the cells incorporated in the scaffold will grow and reproduce, while the scaffold gradually gets broken down. Eventually, the cells grow to replace the damaged tissue and the scaffold disappears.

Other researchers have wondered whether they could grow entire organs or large sections of tissue in the laboratory and then implant them into patients. This, in turn, has led others to contemplate developing improved versions of bodily tissues and organs, which would be tougher and stronger than the natural variety. Could this eventually lead to the development of a real-life Steve Austin?

Collagen copy

One chemist looking to improve on nature is Ron Raines, a professor of biochemistry and chemistry at the University of Wisconsin, Madison, US. In particular, he has been looking to develop a synthetic version of collagen, which is the most abundant protein in mammals and the central material making up

connective tissues like cartilage, ligaments and tendons. It is also a major component of bone, teeth and skin.

Bodily collagen is a tough fibre – around 1.5 nm in diameter and 300nm long – consisting of three intertwined polypeptide strands (forming a triple helix). These fibres, known as tropocollagen subunits, spontaneously self-assemble to form the larger arrays of collagen used in various bodily tissues.

‘We’ve had a long-standing interest in collagen, especially in understanding the fundamental chemical forces that lead to the stability of the collagen triple helix,’ explains Raines. ‘Over the past five to 10 years, we’ve made a lot of progress in revealing those forces and now we can apply that knowledge to problems in biology, especially in biomaterials science.’

The three polypeptide strands in collagen are made up of repeating groups of three amino acids, mainly proline and glycine, and are normally held together by hydroxyl groups. In 1998, Raines and a group of colleagues discovered that by replacing these hydroxyl groups with fluorine molecules they could greatly increase the strength of collagen fibres. Natural collagen breaks down at temperatures above 58°C, whereas Raines’s version was able to withstand temperatures of over 90°C.

Then, in 2006, Raines succeeded in creating synthetic collagen fibres that were longer than natural versions. This was a big step forward, because previously researchers had only been able to synthesise very short collagen fibres (less than 10nm in length). To create their long version, Raines and his team designed a collagen triple helix in which two of the strands contained eight amino acid triplets, while the middle strand contained only three. These strands were joined together at one end and then a further amino acid triplet was added on top.

This additional amino acid triplet acted like a sticky tag and naturally linked up with the short middle strand of another triple helix to form a longer helix. Because this longer helix still possessed a short middle strand and a sticky tab on top, it was free to continue combining with other triple helices. Using this method, Raines and his team found that they could generate synthetic collagen fibres that were over 400nm in length.



‘So now we’re very busy putting these two things together to make triple helices that are both stronger and longer than anything found in nature, as well as developing means to make them on a larger scale,’ says Raines. The first likely application of these strong and long collagen fibres will be wound healing, especially for treating the skin of burn victims. ‘We fully expect to conduct animal testing of the basic wound healing concepts this year,’ Raines predicts.

A very different type of synthetic collagen could eventually result from work on electrospinning and electrospinning being conducted by Suwan Jayasinghe, a biophysicist, and Andrea Townsend-Nicholson, a biochemist, at University College London, UK.

‘Both electrospinning and electrospinning work by charging a liquid medium and accelerating it from a high electrical potential to a lower one,’ explains Jayasinghe. In electrospinning, the liquid medium

is ejected as fine droplets, while in electrospinning it comes out as a long microscopic thread.

What Jayasinghe and Townsend-Nicholson have done is to develop versions of electrospinning and electrospinning that eject living cells in conjunction with the liquid medium (usually a polymer), but without harming the cells in any way. This opens up the possibility of using these techniques to create artificial bodily organs and tissue.

‘Here’s a technique where we can directly deposit living cells as droplets or threads,’ says Jayasinghe. ‘Now, in the case of electrospinning, we deposit cells as droplets on top of each other, like constructing a wall, to build replacement tissue. In the case of electrospinning, we can deposit these threads in accordance with a defined pattern and build a three-dimensional scaffold.’

Bio-electrospinning and cell electrospinning also offer the possibility of creating enhanced versions of biological tissue. At the moment, Jayasinghe and Townsend-Nicholson have only experimented with a medical-grade polymer known as poly(dimethylsiloxane), but the technique could also theoretically work with many other polymers, including natural polymers such as collagen.

‘There are hundreds of polymers out there that are completely biocompatible and can be used for this process,’ claims Jayasinghe. So, for instance, a stronger version of cartilage could potentially be created by using cell electrospinning to generate threads of cartilage-producing cells encapsulated within a tough biocompatible polymer.

The bones of it

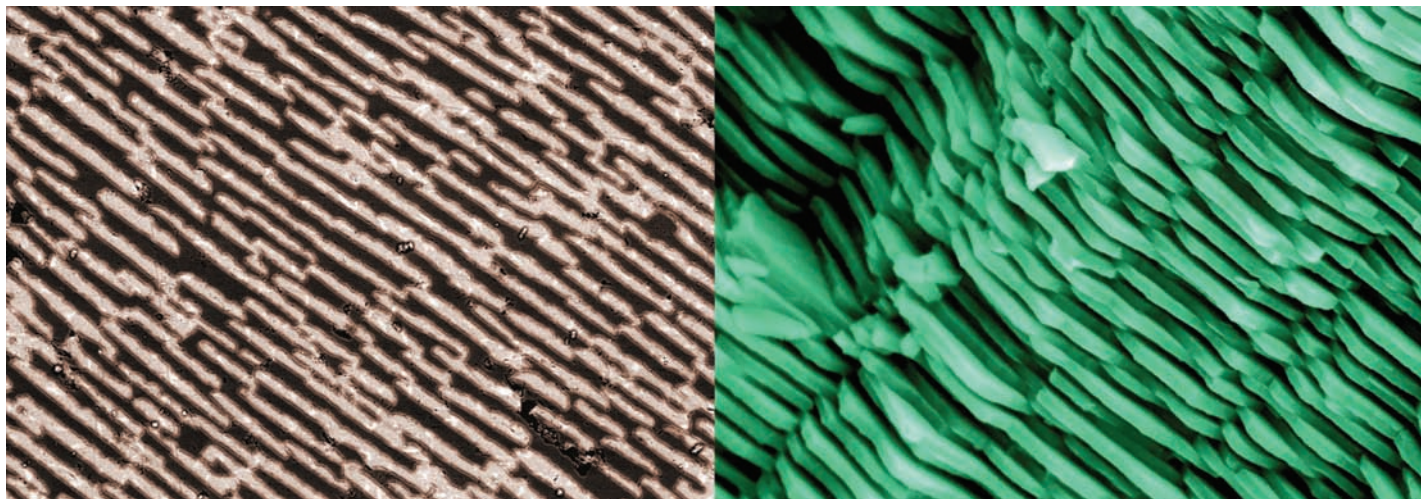
Bone is already an incredibly strong material, but researchers are still interested in the possibility of making it even stronger. At the moment, however, this increased strength is merely a potential side effect of stimulating the growth of new bone.

Although new bone grows all the time, it mainly just replaces existing older bone. Patients who have lost major amounts of bone through disease or injury are unable naturally to replace that bone, meaning that they need to be fitted with metal or ceramic prostheses.

A better alternative would be to try to stimulate the growth of new bone within the patient and a number of researchers have experimented with growing bone cells known as

Like the twisted steel cables of a suspension bridge, collagen triple helices form the scaffold of our bodies. Synthetic collagen fragments can self-assemble into triple helices that are longer than any natural collagen

‘The first likely application of these strong and long collagen fibres will be wound healing’



TONY TOMSIA, LAWRENCE BERKELEY NATIONAL LABORATORY, US

osteoblasts on a variety of artificial scaffolds, including special bioactive glass.

In normal bone, osteoblasts exist within a mineralised organic matrix that they secrete. The inorganic component of this matrix consists of crystalline mineral salts and calcium in the form of a compound known as hydroxyapatite, while the organic component consists of collagen. This combination of a hard mineral component and a tough, flexible organic component helps give bone its great strength.

But if new bone could be grown on an artificial scaffold possessing even greater strength, perhaps the resultant bone will be stronger than the natural variety. This is a possibility that Laura Zanello, as assistant professor of biochemistry at the University of California, Riverside, US, is now exploring by trying to get osteoblasts to grow on a scaffold of carbon nanotubes (CNTs).

One of the great advantages that CNTs have over other scaffold material is that they are both very light and incredibly strong. As such, they are already being added to sports equipment, such as tennis rackets, and car chassis to increase their strength.

‘Carbon nanotubes are considered the strongest material on earth, and have tremendous flexibility, which could protect newly formed bone tissue from breaking (at least in theory),’ says Zanello. ‘In this sense, it would be stronger than natural bone.’

In 2006, Zanello showed that osteoblasts will happily grow on CNTs, although only on unmodified, electrically neutral CNTs. Furthermore, Zanello discovered that these osteoblasts retained the

ability to secrete the mineralised organic matrix that subsequently turns into bone. She is continuing to explore growing bone cells on CNTs, but can’t reveal any further details at the moment.

However, the strength of bone is not simply down to what it’s made of, but also depends on its precise structure. Normal bone consists of numerous layers, in which the collagen fibres are oriented in parallel. This layered structure also gives bone its strength and prevents it from breaking.

Material scientists have found it difficult to synthesise artificial compounds with a similar layered structure, but recently a team from Lawrence Berkeley National Laboratory, California, US, led by Antoni Tomsia, has managed to do it, by taking inspiration from ice. When water freezes, crystals of pure ice form in layers, while any impurities, such as salt, are expelled from the ice and trapped in channels between the layers.

Tomsia and his team found that if they dissolved hydroxyapatite in water and then froze it, the hydroxyapatite would congregate in the channels between the layers. After melting the ice, the researchers were left with a bone-like layered hydroxyapatite scaffold (see images above). As with bone, this scaffold also contained small bridges between the layers, which help prevent fractures.

‘These characteristics contribute to the scaffolding’s mechanical toughness,’ says Tomsia. ‘Cracks don’t propagate as easily and more energy is needed to break the material. This makes the scaffolding four times stronger than the porous hydroxyapatite materials currently used in bone substitutes.’

A porous hydroxyapatite scaffolding (left) can be made with a similar multilayered structure to that of natural nacre (mother-of-pearl) (right)

Tomsia and his team have also filled the gaps in this scaffold with an organic polymer that contains osteoblasts, in order to stimulate new bone growth. In the future, they may be able to fill the gaps with Zanello’s mixture of CNTs and osteoblasts, which could result in an incredibly tough bone-like material.

These bones may then be able to withstand the forces created by the powerful artificial muscles being developed by a team led by Ray Baughman, a chemistry professor at the University of Texas at Dallas, US.

In current artificial limbs, movement tends to be generated by electrically powered motors, but Baughman and his team have managed to develop two types of artificial muscle that can both be powered by liquid fuels. In the first type, hydrogen is used to generate an electric current, which causes a carbon nanotube electrode to repeatedly bend and straighten. In the second type, heat generated by the reaction of hydrogen, methanol or formic acid with oxygen causes a platinum-coated shape-memory wire to bend. It then naturally straightens as it cools.

These artificial muscles are already 100 times stronger than natural muscles, and Baughman claims that they could eventually lead to artificial limbs and hearts powered by food-derived fuels.

So chemists and biochemists are now well on their way to rebuilding a man with stronger bones and connective tissues and more powerful muscles. For the complete *Six million dollar man* effect, they now just need to find a way to recreate the ‘na-na-na’ noise.

Jon Evans is a freelance science writer based in Bosham, UK

‘Carbon nanotubes could protect newly formed bone tissue from breaking’