The lab-grown penis: approaching a medical milestone

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Dr Anthony Atala: ‘We were completely stuck. We had no idea how to make this structure, let alone make it so it would perform like the natural organ.’

Gathered around an enclosure at the Wake Forest Institute for Regenerative Medicine in North Carolina in 2008, Anthony Atala and his colleagues watched anxiously to see if two rabbits would have sex. The suspense was short-lived: within a minute of being put together, the male mounted the female and successfully mated.

While it’s not clear what the rabbits made of the moment, for Atala it was definitely special. It was proof that a concept he’d been working on since 1992 – that penises could be grown in a laboratory and transplanted to humans – was theoretically possible. The male rabbit was one of 12 for which he had bioengineered a penis; all tried to mate; in eight there was proof of ejaculation; four went on to produce offspring.

The media’s coverage of Atala’s announcement a year later was understandably excited. Not just because of the novelty of a man growing penises in a laboratory, but because his work would fulfil a real need for men who have lost their penis through genital defects, traumatic injury, surgery for aggressive penile cancer, or even jilted lovers exacting revenge.

At present, the only treatment option for these men is to have a penis constructed with skin and muscle from their thigh or forearm. Sexual function can be restored with a penile prosthetic placed inside. The prosthetics can be either malleable rods, with the penis left in a permanently semi-rigid state and thus difficult to conceal, or inflatable rods, which have a saline pump housed in the scrotum. Both technologies have been around since the 1970s. The aesthetics are crude and penetration is awkward.

Another option is a penis transplant from another individual, but this carries a risk of immunological rejection. The chance of organ death can be lessened with anti-rejection drugs, but these drugs have serious side-effects. Transplants can also have a psychological impact, especially with an organ as intimate as the penis. In 2006, a Chinese man was the first to receive a donor penis; two weeks after the 15-hour operation, surgeons removed the transplanted organ on the request of both the patient and his partner.

Atala hopes his technique will mitigate both immunological and psychological issues because his penises would be engineered using a patient’s own cells. “The phallus is actually much longer than you think,” he explains. “It goes all the way behind the pelvis, so no matter the extent of the damage, there is a high probability that there are salvageable cells.”

Peruvian-born Atala, a urological surgeon and professor of regenerative medicine, heads a 300-strong team at the institute. He corrects himself constantly, always going back to edit his speech, adding words such as “high probability“ or “in all likelihood” to be sure his sentences are word-perfect. Soft-spoken and mild-mannered, Atala is a trailblazer in the field and you can’t help but think that his measured speech is an attempt to provide a sure path for others to follow.

To some, engineering human organs sounds like science fiction, but for Atala it’s an absolute necessity. As we live longer (and thus our organs fail more) the shortage of organs for donation will only get worse. If he

can work out how to generate the organs people need in a reliable and effective way, the technology can improve a lot of people's lives. In 2006, Atala and his team announced the first successful bioengineered organ transplant, a bladder, which had been implanted into seven patients in 1999. Earlier this year he announced the successful follow-up of four women given bioengineered vaginas in 2005-2008. Despite these successes, he says, the penis is proving trickier.

Organs increase in architectural complexity as they go from flat structures such as skin, cylindrical structures such as the vagina, to hollow non-tubular organs such as the bladder. As a solid organ, the penis tops this list in both density of cells and structural complexity. It consists of a spongy erectile tissue unique to it. During an erection, signals from the nerves trigger blood vessels to dilate, filling this spongy tissue with blood and causing the penis to lengthen and stiffen.

"We were completely stuck," says Atala of the first few years of research in the early 90s. "Even the idea of the field of regenerative medicine was brand new at the time. We had no idea how to make this structure, let alone make it so it would perform like the natural organ." Then, in 1994, he figured he could take a helping hand from Mother Nature. Using a technique pioneered for biological skin dressings, he would take a donor penis and soak it in a mild detergent of enzymes for a couple of weeks to wash away the donor cells.

"You're left with a mostly collagen scaffold – a skeleton if you like, that looks and feels just like the organ," explains James Yoo, one of Atala's collaborators at the institute. "Think of it like a building. If you remove all the furniture and the people, you're still left with the main structure of the building. Then you replace the tenants with new ones. That's the whole idea. It's just that the building is a penis and the tenants are cells."

The next step is to reseed the structure with the patient's own cells taken in a biopsy from salvageable tissue and grown in culture. Smooth muscle cells, which relax during an erection to allow the vessels to dilate and the penis to fill with blood, are first, followed by endothelial cells which line the interior surface of blood and lymphatic vessels. When ready, the bioengineered penis is ready to be transplanted to the recipient.

So why, six years on from successfully engineering a penis for rabbits, have they not yet done the same for humans? Atala explains that, as is often the case with these things, scaling up is proving difficult. "Even though we can make them in a very small mammal, we have to tweak the technology, the processes, the ratio of cells and so on, to get larger and larger structures. That's pretty much what we've been doing since the rabbits."

They've made encouraging progress. Atala has engineered half a dozen human penises. Although they are not yet ready for transplanting, Atala's team are assessing the structures for safety and effectiveness. One machine squashes, stretches and twists them to make sure they can stand up to the wear of everyday life; another pumps fluid into them to test erections. Sliced segments are tested at the genetic, cellular and physiological level.

"It's a rigorous testing schedule," says Atala, wearily. "But we're trying to get approval from the US Food and Drug Administration so we know everything is perfect before we move to a first in-man test."

Neither Atala nor Yoo will be pushed for a date for the first test in man, saying only that they'd expect it to occur within five years. "In the end we're aiming for the entire size of the organ," says Atala. "But in reality our first target is going to be partial replacement of the organ."

In the short term, this would include growing smaller lengths for partially damaged penises, but would also include replacing parts of the penis to help cure erectile dysfunction. Degradation of the spongy erectile tissue, says Tom Lue, a urological surgeon at the University of California, San Francisco, is the leading

cause of impotence in old age. Disorders such as high blood pressure or diabetes can damage the delicate tissue – the resulting scar tissue is less elastic, meaning the tissue cannot completely fill with blood and the penis cannot become fully erect.

“Show me a hundred 70-year-old men with erectile dysfunction,” says Lue, “and I’ll bet you 90% of them have scar material in their penis.” Traumatic injury or priapism, a condition that leaves men with an increasingly painful erection for hours or even days, can also damage the tissue and cause erectile dysfunction in younger men. “If you replace the damaged spongy tissue you can give these men a better erection.”

Engineering the spongy tissue for replacement is one of Atala and Yoo’s interim goals. Lue is also hoping to restore erections, but for less severely damaged penises. For instance, some men become impotent after surgery for prostate or rectal cancer because the nerves that regulate erections, which run through the rectum and prostate into the centre of the penis, can get damaged. Likewise with traumatic injury, if the vessels are severed then the penis cannot fill with blood.

Microsurgery to connect the vessels and nerves in the penis is possible but often ineffective. Lue is testing whether injecting stem cells into the base of the penis can encourage the nerves and cells to rejoin. His work might also help Atala and Yoo to stimulate nerve and vessel regrowth when the day comes for the first in-man trial of a bioengineered penis. Twenty-two years into his research to bioengineer a human penis, Atala is a man who is both excited and impatient for that day. And you’d suspect he’s not the only one.

Bioengineered organs: The story so far…

Bladder

In 1999 the bladder became the first laboratory-grown organ to be given to a human. Atala and his colleagues took cells from a biopsy from seven patients with bladder disease. The cells were cultured and then seeded, layer by layer, on to a biodegradable, bladder-shaped collagen scaffold. After about eight weeks they were transplanted to patients, where the organs developed and integrated into the body.

Vagina

Another pilot study, this time in four women with a rare congenital abnormality that causes the vagina and uterus to be underdeveloped or absent. Using a similar technique to the one used to make bladders, in 2005 they implanted the first vagina. Up to eight years after transplant, all four organs have normal structure and function. This technique could be used to help women following injury or cancer.

Penis and beyond

In 2004, they implanted the first bioengineered urethra into five boys. This technology will help in their work towards reconstructing the penis. Atala and his colleagues are also working on 30 different organs and tissues including a kidney, which could be made using a 3D printer, and tissue for the liver, heart and lung.