CLINICAL DEVICES AND SERVICES

Repair shops

Advances in materials and techniques are restoring damaged body parts to full function.

ORTHONIKA

Andrew Amis (left) and Mario Alberto Accardi in the Biomechanics Lab at Imperial College prepare a robot to test synthetic knee menisci.

ORTHONIKA
Shock absorbers for the body

Imperial College London

For Orthonika, 2017 is a year of refinement. The company will put its prototype knee-meniscus replacement through its paces inside donated knees attached to robots that mimic the forces that normally act on this joint. The goal is to catch any design flaws before the company trials the synthetic meniscus in sheep next year.

The robots are found in the lab of Andrew Amis, an orthopaedic biomechanics specialist at Imperial College London and co-founder of Orthonika. For now, Orthonika is a virtual company; its six directors remotely coordinate the activities of a team of suppliers, designers and manufacturers across Europe and the United States. "One day, we'll have to bite the bullet and start paying rent," says co-founder Dominique Kleyn, who has a background in business development and used to work for Imperial Innovations, the technology-transfer office for Imperial. The directors are now looking for partners to conduct next year's preclinical trials.

Sandwiched between the tibia and femur, the knee meniscus is a C-shaped piece of cartilage that acts like a shock absorber, distributing forces across the knee. Although menisci seem to be perfect candidates for 3D-printed replacements, 30 years of failed attempts to make functioning synthetic versions show that it's not that easy.

When knee menisci tear — typically through traumatic twisting injuries in younger people and following degeneration in older people — little can be done to repair the tissue. A torn meniscus that is causing pain or interfering with knee function is simply removed, but this greatly increases the risk of osteoarthritis.

Amis, whose academic work has led to the development of prosthetic elbows and artificial ligaments, became interested in making replacement menisci about a decade ago. He and another Orthonika co-founder, Justin Cobb, an orthopaedic

surgeon at Imperial, saw it as an "obvious thing to tackle".

In June 2014, having come up with a promising meniscus design and, crucially, a way of attaching the device to the tibia, Amis and Cobb sat down with entrepreneurs from Sierra MedTech, a medical-technology start-up based in the United Kingdom. Orthonika was formed in December of that year.

Sierra MedTech had an innovative approach to constructing orthopaedic implants. The polymer materials that it used were not new, but the company was combining them in a composite that replicated the structure and function of musculoskeletal tissues.

CHANGE OF DIRECTION

Sierra MedTech's directors — including Kleyn and co-founder Mario Alberto Accardi, a venture capitalist with a PhD from Imperial who had helped to develop the new composite — thought that their invention had numerous applications in orthopaedics. But after surveying clinicians, they focused on replacement menisci. Removal of torn menisci is one of the most commonly performed orthopaedic procedures in Europe and the United States. Apart from expensive and logistically difficult transplants, there are no viable replacement options. With the right material but no design, they turned to Amis and Cobb at Imperial.

"We know if we can get this right, there will be a market for it."

Amis says he and Cobb were already looking for commercial partners, but what Sierra MedTech proposed was altogether different from how Amis's earlier research had been developed. Previously, he had taken projects through to the patent-filing stage with the university and relinquished control of the work when the university licensed the patent to large companies. To develop early ideas, he had always secured grant funding. But here was a tiny company wanting to partner early in the development process and to fund it and help steer it. "The idea of Mario and his team coming along and saying, 'We know how to start and grow companies and raise capital', seemed interesting," says Amis. "For me, it's a completely strange and new world."

Accardi describes finding a group of seed investors to "believe in us and the project, and to be willing to take the risk as the key step in establishing Orthonika as a new company". That first £150,000 (US$192,000) of funding gave the company credibility with the university. "That's the life of a biotech," says Kleyn. "You take a little step and that enables you to take a bigger step."

That next step was Orthonika's toughest challenge so far: negotiating an intellectual-property deal with Imperial Innovations, which held the patents arising from Amis's work. It took several months to reach an arrangement that satisfied Imperial and left Orthonika with enough flexibility to be confident that it could attract further investment.

"We had then to draw a wider team around us," says Kleyn, "people who'd help with design work, testing, manufacturing and assembly. It was about finding the right fit." Achieving this has led to the development of the company's prototype, which is currently undergoing testing in Amis's lab.

"There are very few opportunities left in medical technology and orthopaedics that are more or less greenfield with such a high unmet clinical need," says Accardi, "so we know if we can get this right, there will be a market for it."

Orthonika secured a £260,000 grant from Innovate UK in February, and another seed investor matched the investment. These funds cover this year's testing and the initial animal trials. If preclinical testing goes to plan, the company hopes to insert its knee meniscus into a small number of people within four years. If this trial is promising, the co-founders hope that the company will then be acquired by a large orthopaedic device firm. ■

Liam Drew *is a science writer in London.*

CUTISS
Skin grafts

University of Zurich, Switzerland

In a bright and busy lab in Zurich, Switzerland, a square slab of thin gel is lifted from a bath of cell-culture solution. It carries a cargo of dermal and epidermal cells intended to grow into a graft that could transform a burns patient's appearance — and life. The glistening gel is an attempt by Swiss start-up Cutiss to realize the plastic surgeon's dream of artificial skin that can be shaped as required and then grafted onto damaged areas. Its material is about to enter phase II clinical trials.

Cutiss co-founder Ernst Reichmann describes the progress from basic research programme to a spin-off company with a product being readied for market as a long slog punctuated by several breakthroughs. Reichmann, a cell biologist at the University Children's Hospital Zurich, has spent more than 30 years exploring the use of collagen hydrogels as a matrix for growing human cells — with the goal of recreating human organs. "All of a sudden we realized that we could do skin," says Reichmann, describing one of the eureka moments. Although the details of how the skin-like material forms remain elusive, Reichmann suspects that he had hit on procedures that distributed the cells in a manner that supported the proliferation and layer formation of skin cells. "Our clinical collaborators then asked me about expanding the technology and developing it for use on burns patients."

Soon after beginning the first studies in humans, biotechnologist Daniela Marino, Reichmann's colleague in Zurich, took up the challenge of exploring the opportunities for a spin-off company. She pitched the idea to funders and advisory agencies. "We were naive, and the learning curve was steep," says Marino, but she soon obtained initial funding of around 20,000 Swiss francs (US$20,000) from the Swiss government's Commission for Technology and Innovation. Cutiss, from the Latin for skin (with the additional 's' to reflect the focus on creating new tissue), was born.

In 2015, the fledgling enterprise got a boost when it won a Swiss start-up competition called Venture, bringing in 60,000 Swiss francs. Marino says that this was essential for gaining approval from key regulatory bodies and for pursuing further funding. And the prize brought the company to the attention of the Wyss Translational Center in Zurich, a research facility founded by the University of Zurich and the Swiss Federal Institute of Technology (ETH) Zurich, which is now

VALÉRIE JAQUET, UNIV. CHILDREN'S HOSPITAL ZURICH

Cutiss technicians test the production of artificial skin.

UNIVERSITY OF SYDNEY/ELASTAGEN

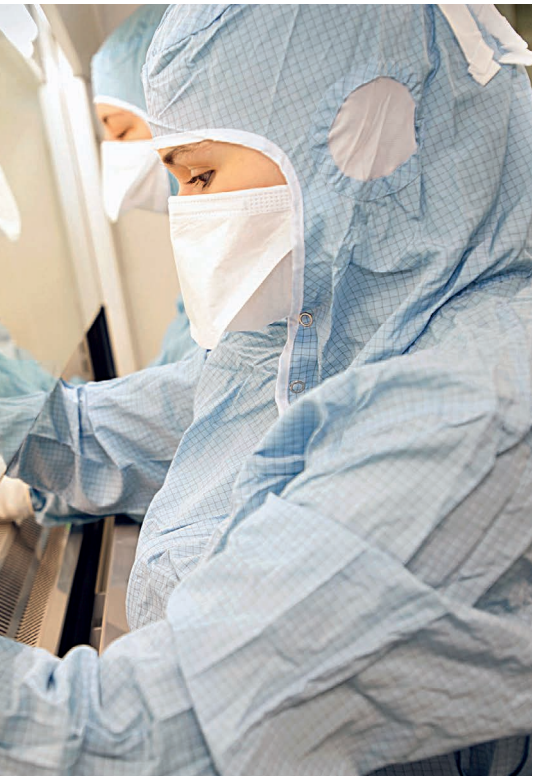
funding the phase II clinical trials. Marino says the outcome of the phase I trial provides "grounds for optimism".

Cutiss's research now focuses on its material's biological limitations. One problem is that the current grafts lack the pigment cells known as melanocytes and so can only produce white tissue that must be tinted with creams to blend in with a recipient's skin. The grafts also lack sweat glands and other specialized components of normal skin. One major advantage the Cutiss grafts have over some alternatives, however, is that they are derived from a patient's own cells and avoid the problem of tissue rejection.

The company intends to have a product that achieves significant reductions in scarring and in the need for repeat procedures compared with existing options in clinical use in 3–5 years. Marino hopes that eventually the firm will offer permanent personalized skin grafts that grow with the patient's body, and that could have more-specialized features such as pigment cells and blood capillaries. This would be a huge advance from the more-limited procedures currently available.

Some clinicians share these aspirations. "This project is a step change for patients with burns," says Naiem Moiemen, clinical service lead for burns at Queen Elizabeth Hospital Birmingham, UK, and president of the European Burns Association. ■

Andrew Scott *is a science writer in Perth, UK.*



Elastagen is exploring materials made from engineered tropoelastin for wound repair.

ELASTAGEN

High-tech wound and tissue healing

University of Sydney, Australia

With initial proof-of-concept financing secured in 2005, Elastagen should be considered a teenager in start-up years. But biotechnology that relies on wet materials rather than software or devices has a much longer road to commercialization. The idea behind the company's offering is even older. In 1995, a research team at the University of Sydney in Australia led by tissue engineer Anthony Weiss announced that it had produced the human form of the molecule tropoelastin in genetically modified *Escherichia coli* cells (S. L. Martin *et al. Gene* **154,** 159–166; 1995). Tropoelastin is the building block of the protein elastin that, together with collagen, gives skin its shape, strength and stretchiness. Elastin is also an essential component of organs such as lungs, as well as of blood vessels. Elastagen is exploiting the unique physical and biological properties of elastin to develop a range of products that support cell growth and tissue repair.

Most elastin is produced in babies in the womb and during childhood; it is one of the body's longest-lasting proteins, with a half-life of more than 70 years. But the drop in elastin production in adulthood means that serious injury or ageing results in inefficient repair processes. Elastagen chief executive Rob Daniels joined the company in 2008. The developmental biologist says that the potential of recombinant tropoelastin was immediately apparent. "It's logical to want to patch up damage with the same material that a tissue is made of," he says. Collagen is a stalwart of the medical industry in wound sealants and surgical products, but elastin was a discernible target.

With so many possible applications of elastin, it was Daniels's job to assess market opportunity and determine where best to focus resources. He was careful to distinguish between what constitutes an interesting research question and what has potential commercial appeal, after accounting for factors such as the scalability of manufacturing processes, pricing and regulatory processes. Moreover, says Daniels, "you've got to build your business in a way that will also provide an exit opportunity for investors." For life-science products, that will generally be within 10 years — a time that is fast approaching for Elastagen, which received Aus$5 million (US$3.8 million) in its first significant round of funding of in 2008.

The company's first target was the medical-aesthetics market. Daniels thought that, with enough funding, it could develop more than one formulation in a reasonable time frame. The company now has products that target three main indications. The most advanced is an injectable gel that makes stretch marks and

acne scars fade away. Another is for surgical scars and will be co-developed with a global medical-devices company that has established marketing and sales channels in numerous countries. The third application is in wound repair. "We'll be looking to enter the clinic at the end of the year with that product," Daniels says.

During the early stages of raising capital, seed funds were generated with a grant and research and development tax credits from the Australian federal government. The New South Wales government's medical-devices fund provided backing that allowed Elastagen to bridge the 'valley of death' while it developed its prototype. This period imperils many spin-off companies before they become attractive to commercial investors.

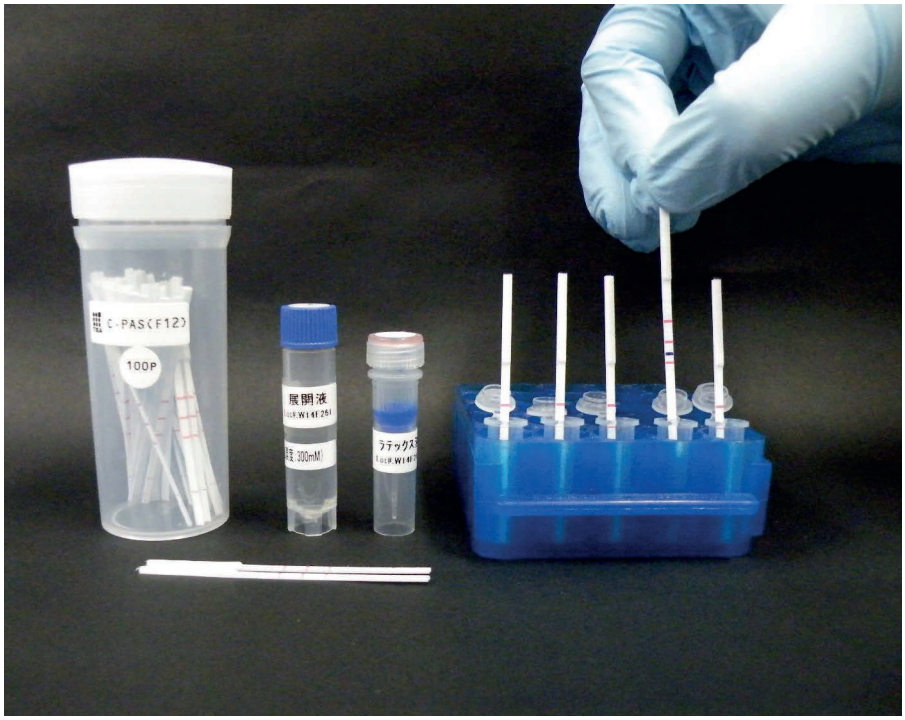
Trust and commitment were also key. Initially, says Daniels, Elastagen "lacked the right mechanism to move the intellectual property comfortably out of the university". But in 2014, as the university's confidence in the company's ability to commercialize increased, the university traded its intellectual property for equity. Owning the intellectual property was necessary for the company to attract additional external investors such as the UK Wellcome Trust, which is now a company shareholder. Daniels says that the transfer could have been faster, but he understands the need to show that the intellectual property is going into the right hands.

Academic culture is also a common stumbling block, says Weiss, who continues to conduct the fundamental research that underpins Elastagen's core assets. In particular, he says, universities are having their success measured, in part, by how much external revenue they generate — a metric that may favour technology licensing because it's a quick road to financial return. "The culture is slowly changing, but there needs to be the right rewards and recognition," he says.

> ***"The culture is slowly changing, but there needs to be the right rewards and recognition."***

Weiss adds that although academic institutions might recognize the importance of a particular discovery, they also need to acknowledge that the technology will start having a real-world impact only once it is out of their hands. "When it's time to refine a product and make the production process robust, it's the time to let go," he says. "This is when you have to get the right chief executive and smart business-minded people involved." ■

Branwen Morgan *is a freelance science writer in Sydney, Australia.*



TOHOKU BIO-ARRAY

Tohoku Bio-Array's membrane strips can be used to detect DNA from pathogenic organisms.

TOHOKU BIO-ARRAY

Fast-forwarding DNA detection

Tohoku University in Sendai, Japan

Imagine deciphering the source of an infectious-disease outbreak, a crop disease or a rare genetic variant present in a person's genome, all in less than one hour. This is what biotech start-up Tohoku Bio-Array, a 2013 spin-off from Tohoku University in Sendai, Japan, is trying to turn into a reality.

Tohoku Bio-Array's technology quickly identifies DNA using a tagged DNA primer or tag sequence printed on a membrane strip. DNA extracted from a target pathogen first goes through a standard tagged primer polymerase chain reaction (PCR) protocol aimed at the disease-causing agent. The membrane strip does the rest: if the PCR product contains a fragment of DNA that matches the sequence of the complementary tagged DNA on the membrane, it produces a positive result. The protocol is simple — the membrane strip just needs to be placed into a tube containing the PCR-amplification product.

The company's DNA-testing strips will allow health-care workers to identify the source of a disease within one hour, says founder and biomedical engineer Mitsuo Kawase. "Our goal is to contribute to the eradication of infectious diseases in the world by providing a quick and accurate method to identify pathogens," he says. The company sells membrane strips for testing kits that detect diseases such as Dengue, Zika virus and tuberculosis. Its sales in 2016 hit ¥40 million (US$360,000).

The researchers at Tohoku Bio-Array think that the membrane strips are a viable option for pathogen detection in places or situations in which infrastructure is lacking. A strip that can detect four types of DNA costs just ¥500 and is sold to manufacturers of DNA-testing kits.

Although the technology is intended for health-care workers to identify the pathogens behind a disease outbreak or to diagnose the risk of developing a condition, the potential applications go beyond health. Tohoku Bio-Array also designs membrane strips that can detect pathogens present in recently hatched shrimp, so that unhealthy individuals can be discarded. As long as the target DNA sequence is known, tagged DNA can be designed for almost any species and printed on the membrane.

The company is working with other Japanese universities to design DNA tags to identify other diseases, including HIV/AIDS and malaria. Kawase also plans to refine the technology so that one strip can detect a wider array of pathogens and to design membrane strips that don't depend on post-PCR DNA. That way, Kawase says, pathogens could be identified in blood, sputum or urine. ■

Karl Gruber *is a freelance writer in Perth, Australia.*