University of BRISTOL

2009 CENTENARY

GREAT PAST ~ GREATER FUTURE

re:search

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The Enterprise Culture

The University of Bristol is a research-intensive university of international standing, with a reputation for excellence. It also leads on the UK's university enterprise agenda, building on research and education to deliver benefits both to the local community and to the UK knowledge economy.

With that in mind, we aim to equip future entrepreneurs with the inspiration and skills to create and grow successful business ventures. We therefore provide a range of training programmes for staff, researchers, postgraduates and undergraduates, covering all aspects of starting and developing a new business venture. In particular, we offer students the opportunity to get a feel for business through BUBA (Bristol University Business Angels), a student-run company with up to £30,000-worth of financial support from the University. It provides a unique opportunity for students to run their own business, offering genuine 'real life' experience. In addition, a week-long course gives students the opportunity to understand how to create innovative business ventures or projects with companies. Run by experienced entrepreneurs with international experience, the highly interactive school provides a series of sessions covering all aspects of business operations and strategy.

Students, staff and graduates are also encouraged to enter the New Enterprise Competition by submitting a business plan for the creation of a new company. In reading this issue of *re:*search, it is inspiring to see how many of the research groups featured here have got their company off to a flying start by winning the competition. To help turn their ideas into reality, the winners are given a substantial cash prize, mentor support and the provision of office space at the Bristol SETsquared Acceleration Centre.

The University now boasts a portfolio of over 140 patents and 100 patent families, more than 120 active licences, and 20 spin-out companies. In the past year, these companies attracted nearly £25 million in new investment, a significant proportion of which went back into the University to support research; thus it is an important source of research funding. The University's holdings in spin-outs and other companies engaged in exploiting new technologies emerging from research at Bristol are managed by Bristol Innovations Ltd, a company wholly owned by the University.

This issue focuses on a few of those spin-out companies, looking at how their success grew out of the research generated at the University and how, in turn, that research has been commercialised. Not only do we hope you will find these articles interesting in their own right, we also hope they might inspire those thinking about a new business venture to take that crucial first step forward.

Derek Pretty
University Registrar and Chairman of Bristol Innovations Ltd

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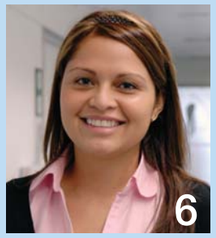
Full details of all spin-out companies from the University of Bristol can be found at: www.bristol.ac.uk/research/newco/spinouts



pre: view

The Null

Null Hypothesis, the Journal of Unlikely Science, is an online science magazine that approaches science communication in a unique, fresh and non-exclusive fashion. Since coming second in the University's New Enterprise Competition in 2005, the Null, as it is fondly known, has migrated from paper to the web, a medium well suited to debunking the myth that scientists are dull and boring. Developed by three postgraduates from the School of Biological Sciences, the Null was described by the *Daily Telegraph* as the *Private Eye* of science.

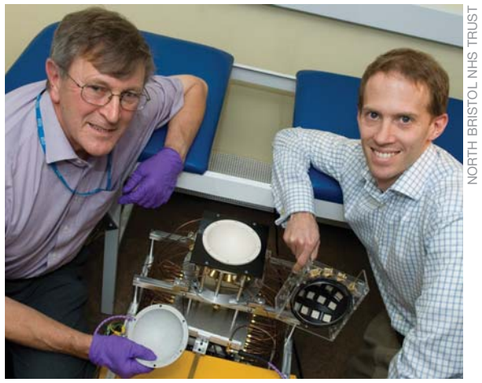
"Science in the UK labours under a stuffy image and government figures show that students are turning away from it in their droves," said Dr Mark Steer, co-founder. "As academics we wanted to challenge the current image of science in the media by highlighting the weird and wacky side and proving that science can be enjoyed by anyone."

Developed by three postgraduates from Biological Sciences, the Null was described by the *Daily Telegraph* as the *Private Eye* of science

So what does null hypothesis actually mean? Loosely speaking, it's the scientific equivalent of randomness; more accurately, it's a statistical hypothesis that can be tested and refuted to support an alternative hypothesis. As Wikipedia elaborates: rejecting the null hypothesis does not show that any particular alternative hypothesis explains the data; merely that it is reasonable to devise alternative hypotheses that may explain the data better. Got that? ■

www.null-hypothesis.co.uk

Professor Alan Preece, left, with Dr Ian Craddock.



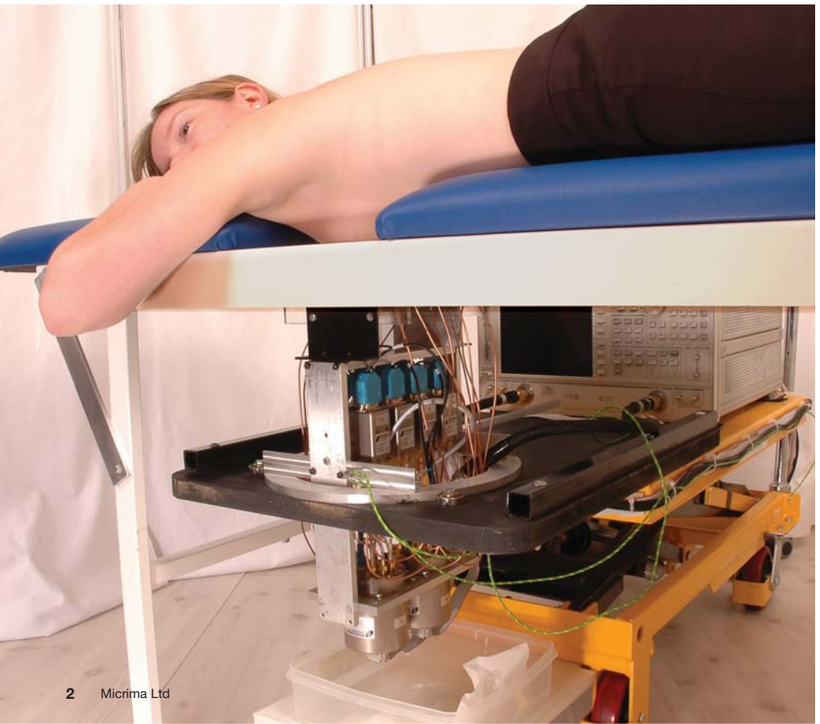
NORTH BRISTOL NHS TRUST

A chance conversation between Alan Preece, Professor of Medical Physics in the Bristol Oncology Centre, and Dr Ian Craddock from the Department of Electrical and Electronic Engineering has led to the development of MARIA, a new and safe technology using radio waves to image breast cancers.

How do you solve a problem like MARIA?

Each year there are over 41,000 new cases of breast cancer in the UK alone. The disease is the most common cause of death in European women aged between 35 and 59. Early detection greatly improves a woman's chances of survival. For example, mammograms have been shown to lower the risk of dying from breast cancer by 35% in women over the age of 50 and by 25-35% in women between 40 and 50. Finding breast cancers early also means that many more women are able to keep their breasts. When caught early, localised tumours can be removed without resorting to breast removal. However, mammograms still miss 15-20% of breast cancers that are simply not visible using this technique, and the younger a woman is, the less likely it is that a tumour will be detected.

Finding breast cancers early means that many more women are able to keep their breasts



The breast is made up of fat, fibrous tissue and glands. Using X-rays, it is difficult to see a clear separation between normal fibrous and glandular tissues and cancerous tissue, as their densities are very similar. In older women, however, the fibrous and glandular tissues diminish, leaving only fatty tissues. Mammography in these fatty breasts is therefore very effective because even small cancers show up well in fatty tissue. An ability to identify cancers in the dense breast tissue of younger women would, however, save many more lives.

Back in the 1990s, Alan Preece was researching the treatment of breast cancers with microwaves. In order to do this he needed to measure the electrical properties of breast tissue. "That's when I realised there was a potential for imaging," says Preece. "So I attempted to look for abnormalities by mapping the breast using our measurement equipment, which was basically a hand-held probe. But at that time the equipment just wasn't sensitive enough to detect small tumours." Ian Craddock picks up the story: "The important thing was that Alan's research had established that tumours have different electrical properties from the surrounding tissue, which implied that it should be possible to image the breast by detecting this difference. My group, at that time, was involved with a remote sensing project for imaging landmines, which is also based on detecting differences in electrical properties – in this case between the landmine and the surrounding soil."

A volunteer demonstrating the new breast imaging technique called MARIA.

Like many developments in science, it was a chance conversation that brought together Craddock's radar approach with Preece's background in dielectric measurement and characterisation of tissue, and they quickly realised there was a way forward together. Early funding was provided by the Engineering and Physical Sciences Research Council, the Trustees of United Bristol Hospital and the University Enterprise Fund. The technique was initially validated through highly sophisticated computational models before moving on to experimental validation in 'phantoms' (physical models of the breast using simulated tissues with known dielectric values for skin, fat, and tumour). Initially, phantoms were made of play dough and gelatine, however, it was not possible to replicate the complexity and variation of real breast structure and the team moved as swiftly as possible to human breast imaging. Preece and Craddock are particularly grateful to the 20 women volunteers from the University who helped them at this crucial stage, advising on whether their prototype was reasonably dignified and comfortable.

When results from these tests looked promising, in January 2006, the company Micrima was formed and 'spun out' of the University, and within no time it had won a prestigious award for innovation from the Institution of Engineering and Technology. The scientists, not used to the world of commerce, found dealing with investors a new challenge: "You've got to be very truthful, absolutely strictly honest in the way that you deal with them, but at the same time you mustn't appear pessimistic," explains Preece.

No easy task when things are still at the developmental stage. But clearly they were successful, for early in 2008 the company secured further funds worth £2 million, raised from a syndicate of co-investors.

The new system, called MARIA, is a breast imaging technique that captures high-resolution, 3D images through the use of harmless radio waves

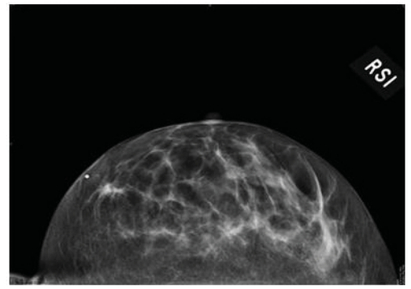
The new system, called MARIA (which stands for Multistatic Array processing for Radiowave Image Acquisition), is a breast imaging technique that captures high-resolution, 3D images through the use of harmless radio waves. An array of small antennas – similar to those inside a mobile phone – is placed around a breast-shaped cup, into which the breast is placed while the woman lies on her front. The signal is transmitted from each element in turn and is then received by all the other elements, effectively 'sweeping' across the breast.

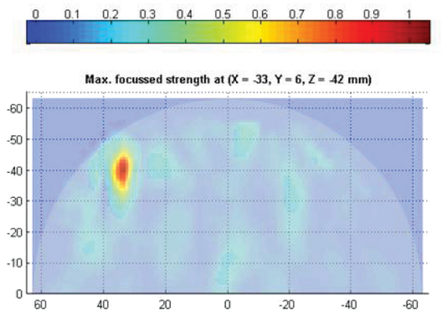
The electrical difference between the different types of breast tissue causes a reflection that produces a 3D image which, in principle, can detect tumours as small as two millimetres across. The smallest tumours detected by X-rays are also about this size but, unlike mammography, MARIA does not require breast compression, making the whole process far more comfortable. The transmitted radio wave signal has a power of less than one milliwatt – far below the safety limit for exposure to radio waves – and hence the technology is intrinsically safe and, unlike X-rays, can be repeated as often as necessary. Initial blind trials with volunteers from a screening clinic have shown MARIA to compare very well with current X-ray technology, correctly identifying all participants with anomalies and 'clearing' all healthy volunteers.

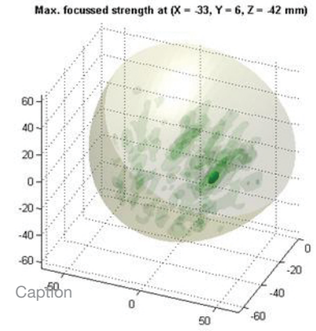
Today, Micrima has just embarked on a new clinical trial in symptomatic patients that is producing its own challenges, particularly with regard to the difficulty of dealing with the very large variation in breast sizes. Volunteers on the first trial came from the NHS screening programme and so were, by definition, over the age of 50, with quite large, fatty breasts. The new trial, however, includes younger women who have found a lump by self-examination, and these younger women have smaller, denser breasts. "It is a significant challenge," says Craddock. "We've seen about 65 patients so far and I think it would be fair to say that no two women have been the same shape or size."

The implications of the new technology are far-reaching. In particular, the compact size and low cost of MARIA will make it ideal for use in numerous alternative locations such as GP surgeries, diagnostic centres and mobile screening units, as well as in developing countries where the cost of screening with X-rays is a major barrier to its widespread use. ■

www.micrima.com





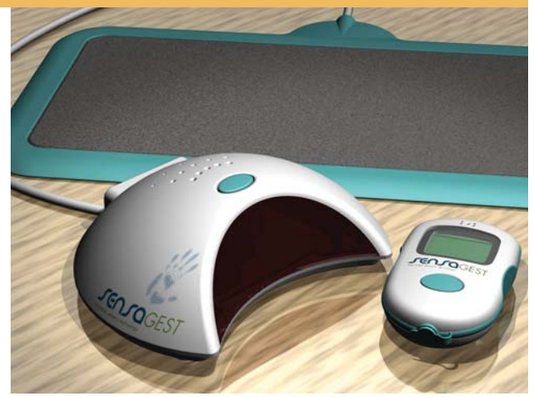


Images of the same breast taken by X-ray (left) and by MARIA (bottom left) which can also be displayed in 3D (bottom right).

Caption

Harnessing the entrepreneurial spirit

Almost all successful businesses have to have some research behind them, whether it's done by a lone individual inspired by a great idea, or by a group working for years on something that slowly becomes viable. Research done in universities is increasingly recognised as a gold mine for generating new business opportunities, so each year the University holds a competition to find the best ideas.



Announcement of the winners of the New Enterprise Competition is one of the highlights of the University's calendar. A dinner, attended by leading members of the Bristol business community, is held in the University's spectacular Great Hall, during which the winning companies are declared amid much whooping of delight, and the successful staff or student team steps up to the podium to thank their supporters and claim the prize. And the prize, sponsored by local businesses, is certainly worth having. The total prize money comes to over £35,000. In addition, a special cash prize goes to the best entry led by an undergraduate student and this year there will be prizes for the best social enterprise scheme, the best medical or healthcare venture, and the best chemistry-based idea.

But cash isn't all they win. An important part of the prize is a chance to give the business a professional front and develop plans away from the normal academic environment. To help them achieve this, rent-free office space is provided for six months in the SETsquared Centre where business guidance and mentoring, as well as access to its high-calibre network of experienced entrepreneurs, potential investors and business professionals, are also available. It's a fantastic opportunity to set a young company on the road to success.

Winners over the past few years have been an interesting mix, as this issue of *re:*search shows, ranging from an innovative design for strong, lightweight, carbon-fibre folding bicycle frames, to Pure Ability Ltd, which developed a state-of-the-art call system to attract the attention of a nurse, and that can be operated by people with minimal hand movement.

For many of the competition winners, the prize fund is not the main goal. More importantly, winning the competition is the first stage in attracting investors and mentors who can help the business rocket from initial idea to a fully-fledged growing business. Ian Anderson, now Chief Executive Officer of Pure Ability, explains how his company got off the ground: "When you break an arm or a leg, life as you know it may pause but it will quickly resume as the plaster comes off. However, when you break your neck, removing the plaster and callipers is just the beginning of the long road to readjustment.

"I broke my neck ten years ago in a road traffic accident. This meant I had to change my job, my home, my car, whilst adjusting to life in a wheelchair. I decided that the best way to tackle this was with a change of direction, so I applied for a computing degree course at the University of the West of England. After completing this course, I came to do a PhD in the field of mobile and wearable computing in the Computer Science Department at the University of Bristol. It was while doing this research that I began to think about how mobile and wearable computing technology could address some of the issues that I, as a wheelchair user, encounter on a day-to-day basis. However, it wasn't long before I realised just how big the gap is between a good idea and a successful business.

"First we had to secure some initial funding so we could begin to develop our ideas, so we entered the 2006 Bristol New Enterprise Competition – which we won – and within a week we had formed the company Pure Ability Ltd. We have a simple aim – to promote independence – and to this end we have developed

Winning the competition is the first stage in attracting investors and mentors who can help the company rocket from initial idea to a fully-fledged business

"I broke my neck ten years ago in a road traffic accident. This meant I had to change my job, my home, my car, whilst adjusting to life in a wheelchair. I decided that the best way to tackle this was with a change of direction…"

touch-sensitive interfaces for enabling the control of domestic devices. In effect, we have replaced buttons with gestures that can easily be performed by people with minimal hand dexterity." 'Sensagest', the company's first product, replaces existing nurse call systems with an intelligent touch-sensitive fabric panel. Instead of pressing a button, the user enacts a simple gesture on the panel; for example, stroking it from one side to the other, or tapping the panel. Wearable computing technology then decodes the gesture and relays a message to a paging device carried by a designated member of staff. Sensagest also has the ability to control devices situated around the bedside.

"Looking back, I find the fact that I am now solving problems I first became aware of when I broke my neck a little strange because I didn't set out to do this. But when I think about it, this is what being an entrepreneur is all about – fusing knowledge with personal experience," muses Anderson.

And where are they now? Within a year of the company's launch, Sensagest had won two Medical Future Innovation Awards – one in the Best Patient Independence Innovation category, as well as the overall prize in the Bone and Joint Innovation category. The Medical Futures Awards are a national showcase of clinical and commercial excellence that help encourage, support and reward new ideas and advancements in healthcare that improve people's lives.

Thanks to winning the New Enterprise Competition, Pure Ability continues to go from strength to strength, driven by a man with a mission

Thanks to winning the New Enterprise Competition, Pure Ability continues to go from strength to strength, driven by a man with a mission. "We plan to develop our technology and provide new solutions that will bring independence to users, both in hospital and in their homes", says Anderson. "We really want to make a difference." ■

www.pureability.com

To enter the next competition, send in your entry by 12 noon on 24 February 2009. For details see: www.bristol.ac.uk/research/newco/competition

Back in December 2003, *re:*search reported on the work being done by Anthony Hollander, Professor of Rheumatology and Tissue Engineering in the Department of Cellular and Molecular Medicine, who was pioneering regenerative medicine techniques in order to replace cartilage in the knees of osteoarthritis sufferers. Five years later, *re:*search reviews the remarkable developments that have occurred in that time.

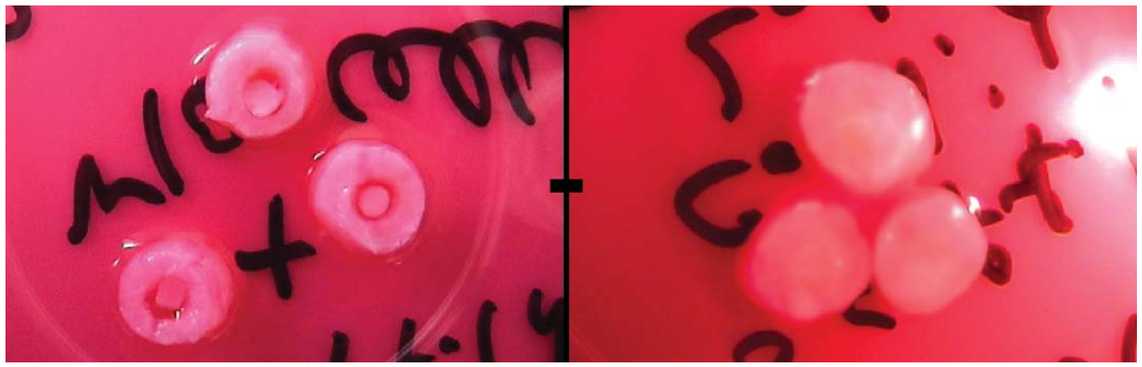
A stem cell bandage for your knee

Building on his previous work, Hollander and his team, which included Dr Wael Kafienah and Dr John Tarlton, announced in 2005 they had, for the first time ever, successfully grown human cartilage from a patient's own bone marrow stem cells. It took just over a month to grow the cells into a half-inch length of cartilage and tests showed that the laboratory-grown cartilage was of a higher quality than any previous attempts at tissue engineering. Now the challenge was how to implant the engineered cartilage into the knee and get it to integrate with the surrounding tissue. The idea was to use cells to drive integration of one tissue with another, with the long-term aim of developing a way of fixing and integrating engineered cartilage with natural cartilage, literally 'knitting' the two surfaces together with cells.

Hollander and his team announced in 2005 they had, for the first time ever, grown human cartilage from a patient's own bone marrow stem cells

Once funding was in place the team pursued this challenge, but it was soon discovered that if cells were left to their own devices, they tended to clump together forming bridges between the two surfaces, but leaving gaps between the bridges. "We had to figure out how to stop these cells clumping," says Hollander. "What we needed to do was keep cells between the two surfaces long enough for them to migrate from one side to the other, but not long enough to form new cartilage – I call it space removal." What was needed was some kind of material that could be seeded with cells on both sides so they could be delivered to each of the two surfaces. It took quite a bit of time to find the best material for this, but once it was identified, the technique worked well very quickly. Using fluorescent labelling, cells could be seen migrating out of the cell 'bandage' and into the surrounding tissue where they soon became integrated. Problem solved.

Having been so successful, the next step was to think about how this procedure could best be exploited. Although the technique had been developed for implanting engineered cartilage, the team soon realised that there was another really important clinical challenge for which this could be a perfect solution.



Left: a plug has been taken out of three pieces of cartilage and then replaced with no further treatment. Right: in each of the three pieces a cell bandage has been inserted between the replaced plug and the surrounding cartilage and then cultured for one month. There is clear evidence of healing in these treated pieces.

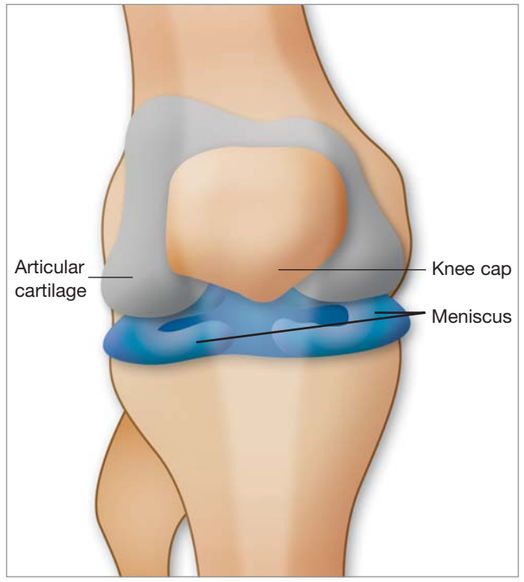
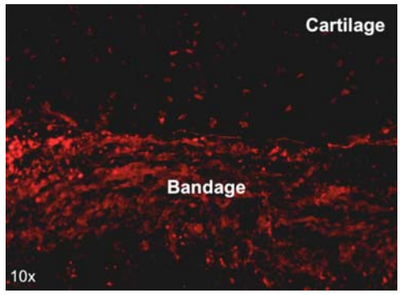


Diagram of the knee joint showing the meniscal cartilage.



Cells were pre-labelled with a red dye before placing them onto the bandage which was then inserted between pieces of cartilage and cultured for one month. Labelled cells can be seen inside the surrounding cartilage, showing they have migrated into it.

A section of two pieces of mensical cartilage (dark blue, top and bottom) integrated together by a cell bandage (turquoise).

Many people aged between 20 and 50 who are active in sport suddenly get knee pain, go to an orthopaedic surgeon and are told they have a torn cartilage. In fact, what this usually means is that there is a tear in the meniscal cartilage – not the white shiny cartilage at the ends of your bones that Hollander usually works on, but the cushion between the two bones of the knee joint that is chemically and structurally slightly different from normal cartilage. Blood vessels around the edge of the cushion provide a supply of blood to the meniscus, and when a tear occurs in that area it can be repaired by sewing it together. However, most tears occur in what is called the white zone – the avascular zone – where there is no blood supply. These tears can be sutured together and the pain relieved for a short time, but when the suture falls out, it is back to square one. Essentially, these tears do not heal, so surgeons routinely perform a partial meniscectomy, removing the damaged part of the meniscus. Unfortunately, in at least 50 per cent of cases, patients go on to develop premature osteoarthritis in the damaged knee, often at an age when they are too young to have joint replacement. It is a significant problem for which there is currently no treatment.

Although the technique had been developed for implanting engineered cartilage, the team soon realised that there was another really important challenge for which this could be a solution

Recognising that there was an unmet clinical need in repairing torn meniscal cartilage, Hollander and the team reasoned "that if we could get our cell bandage into the tear and suture up around it, that would promote healing and we wouldn't have to cut out the damaged tissue". They first filed a patent and then, with some early stage funding from the University, explored the idea of meniscal repair *in vitro*. Despite the results looking very promising, trying to raise money for the next stage took an inordinate amount of time. At last it all came together with a mixture of funds: a Wellcome Trust University Translation Award, designed to assist universities advance ideas with commercial promise in the biomedical area; a grant from the Research Council Technology Strategy Board, intended to support the commercialisation of research; and private funding from investors. In December 2007, Azellon was registered with Companies House.

A pre-clinical model is now under way and the team intend to start a human clinical trial in a year's time. Hollander, now Azellon's Scientific Director, jokes, "So at the moment we are a spin-out company that has no product and nothing to sell, but if the clinical trial goes well then value will be added very quickly". Indeed it will. And he doesn't intend to stop there: tendon, ligament and possibly muscle repairs are already being considered, as well as non-union bone fractures which are not healing, a very serious issue that can lead to loss of the limb. The future looks very bright, both for Azellon and the long-suffering patients these exciting new techniques will be able to treat. ■

www.bristol.ac.uk/cellmolmed

A pre-clinical model is now under way and the team intend to start a human clinical trial in a year's time

Although the stem cell techniques developed by Hollander and commercialised by Azellon are not exactly those that transformed Claudia's life, the bone marrow stem cells used in cell bandages are the same as those used to treat her.

Claudia's story

One Sunday lunchtime in March, Anthony Hollander received a call from his colleague Martin Birchall, Professor of Thoracic Surgery: "I was having a pub lunch with my family when Martin rang me about this woman who needed a new windpipe," says Hollander. "My first reaction was that it was crazy to think we could put together a plan to save her in just a few weeks. My second was that it was a chance to prove that what we had been saying for so long was actually true – that you can use tissue engineering and adult stem cells to make a difference to patients' lives."

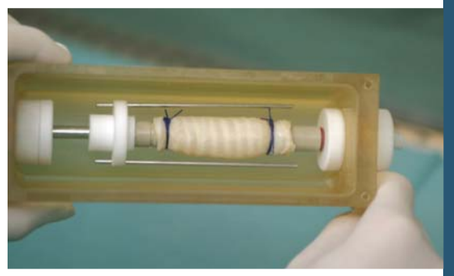
Claudia Castillo had spent years in and out of hospital after a rare form of tuberculosis blocked her airways, making breathing increasingly difficult

Claudia Castillo, a young Colombian mother of two now living in Barcelona, had spent years in and out of hospital after a rare form of tuberculosis blocked her airways, making breathing increasingly difficult. Professor Paulo Macchiarini, Head of Respiratory Surgery at the Hospital Clinic de Barcelona, who has collaborated with Birchall for many years, offered her the possibility of a cure with a procedure never before carried out on humans. In a pan-European effort, the team set about creating the first tissue-engineered trachea, using the patient's own stem cells.

Building on successful laboratory work previously performed by the team, it was proposed that the lower trachea and the tube to the patient's left lung (bronchus) should be replaced with the bioengineered airway, based on the scaffold of a human trachea. A seven-centimetre tracheal segment was donated by a 51-year-old transplant donor who had died of cerebral haemorrhage – Spain has a policy of presumed consent for organ donation. Using a new technique developed in Padua University, the trachea was decellularised over a six-week period so that no donor cells remained.

Adult stem cells were obtained from Claudia's own bone marrow, grown into a large population and matured into cartilage cells (chondrocytes) in Birchall's lab in the Department of Clinical Veterinary Science, using an adaptation of the method devised by Hollander for treating osteoarthritis. The donor trachea was then seeded with chondrocytes on the outside, using a novel bioreactor that incubates cells, developed at the Politecnico di Milano, Italy, allowing them to migrate into the tissue under conditions ideal for each individual cell type. In order to replicate the lining of the trachea, epithelial cells were seeded on to the inside of the trachea using the same bioreactor.

Four days after seeding, the graft was used to replace the patient's left main bronchus. The operation was performed by Macchiarini on 12 June 2008, at the Hospital Clinic de Barcelona. Just four days after transplantation, the graft was almost indistinguishable from adjacent normal bronchi and ten days after the operation Claudia was discharged from hospital. After one month, a biopsy elicited local bleeding, indicating that the blood vessels had already grown back successfully.



The scaffold trachea in the new bioreactor, prior to reseeding with stem cells.

The alternative for Claudia was to remove her left lung, which would have left her impaired for life. However, making the decision to be the first person ever to have such a new and radical operation was a tough choice. "It really is a miracle," she says. "The problem has gone. I made the right decision. I can go to the park and I can play with my children. I hope to start back at my job as a dental nurse in the New Year. I now have a future to look forward to." The science behind her operation marks a new era in medicine. ■

HOW DEEP IS A DEEP HOLE?

Far left: Professor David Smith. Left: Dr Ed Kingston.

Deep hole drilling sounds like a technique that would be used in the oil industry for extracting oil from kilometres inside the Earth. In fact, it is a means of measuring residual stress in complex engineering components, and the holes drilled are only a few centimetres 'deep'. VEQTER Ltd is a leading-edge spin-out company employing this unique technology, as Managing Director Dr Ed Kingston explains.

Residual stresses are introduced into any component that is manufactured. Take a pipe that's made by welding two sections together. As the hot weld metal cools, it pulls on the two sections of pipe until the weld metal in the centre is under tension. The stress created is what is known as a residual stress, and it can be both detrimental to the life of a product and, perhaps rather surprisingly, beneficial. The rivet holes in an aeroplane wing, for example, are sites of high stress that could cause the wing to fail. In order to avoid this, compressive residual stresses are added to the wing to prevent cracks growing. There are many such industries, from nuclear power plants to the manufacture of submarines, where knowing just how large the residual stresses are in a component is crucial to its safety; but until recently they have been extremely difficult to measure and consequently are poorly understood.

In 1998, Kingston worked for the University for two months over the summer, while trying to find a job after finishing his degree. He was supervised by David Smith, Professor of Engineering Materials in the Department of Mechanical Engineering, "And it wasn't long before David asked me to do a PhD," Kingston says. "But I said no! I wanted to work and earn some real money. However, during the summer I really enjoyed it. I particularly enjoyed not being a student anymore, so I carried on and eventually I agreed to do a PhD." Four years later, so much of Kingston's research had been commercial work that he wasn't able to include some of the data in his PhD because they were too confidential. Without realising it, he had started a business.

In 2003, Kingston and Smith put together a business plan and came second in the University's Enterprise Competition, winning £6,000 in cash, plus £1,000-worth of legal advice from Osborne Clarke solicitors. It was enough to get them started and the following year they formed VEQTER. They haven't looked back since.

Today VEQTER is the only company in the world carrying out deep hole drilling commercially. The technique involves drilling a small hole, about three millimetres in diameter and up to 750 millimetres in depth, through the component under investigation. They then measure the diameter of the hole using an air gauge which is accurate to within two thousandths of a millimetre. These measurements, taken in many locations, provide the shape of the hole in its stressed state. They then cut around the outside of the hole, taking out a tube of material. In doing so, the residual stresses are released and the hole changes shape as it relaxes.

By measuring the hole again, at exactly the same locations as before, they can compare the stressed shape of the hole to its unstressed shape and calculate what the residual stresses are through the entire thickness of the component. It sounds relatively simple, but the clever bit is in the development of their advanced analysis tools. These, coupled with the company's extensive expertise in understanding residual stresses, means VEQTER can advise on the management and mitigation of residual stresses in circumstances where they are expected to be detrimental to performance. In doing so, they help to improve the safe working conditions of highly complex industrial components and also reduce the frequency and duration of downtime that can cost some clients more than £1 million a day. ■

www.veqter.co.uk

Chips with everything

While the technology to make computer chips smaller and cheaper progresses each year, the fundamental structure of the chip – the computer architecture – has remained the same for decades. This led Professor David May in the Department of Computer Science to think about what a computer chip should look like for the twenty-first century. Today, his technology has unified the hardware and software worlds into one environment, such that hardware *is* software.

Take a look around and you will soon realise that you are surrounded by small computers – in your mobile phone, your iPod or music player, your TV and wireless network and, of course, in the computer on your desk. But there are many others, embedded and invisible, in lighting systems, security systems and your car. The number of embedded computers is growing exponentially each year, but they are often based on ideas that are decades old. A new architecture only comes along occasionally, but when it does, it heralds tremendous changes.

Back in 2000, it was becoming clear to David May that although the cost of new electronic designs was increasing – along with the time needed to complete designs – the new market opportunities would require a wider range of products that could be rapidly adapted as fashions changed. This led him to think about how electronic systems could be built in the twenty-first century and whether standard electronic components could be adapted to specific needs simply by programming, thereby providing customisation before, at, or even after the point of sale.

new idea in 2000 was to find a way to design electronic systems as collections of small programmable computers, at a cost and power consumption low enough for them to be embedded in toys or even clothes.

"Research in computer design is an interesting concept, as there are many different ways of acquiring knowledge and pushing back the boundaries of our understanding," says May. "Computer science, and computer architecture in particular, really is a different kind of activity as it is more focused on creating and building things than on scientific investigation. The difficulty is that many of the things we design are so complex that we have to employ scientific methods to understand how the design will work, and even how to understand them after we have built them. It is sometimes said that we are engaged in the science of the artificial."

The first draft of the new computer architecture used a large array, a 'sea', of low-cost processors on a chip that would be configured in the software,

His new idea in 2000 was to find a way to design electronic systems as collections of small programmable computers

May's early ideas – over 30 years ago – were inspired by research on robotics and on looking at how collections of small computers could be used to build intelligent systems; how they could communicate with each other and, just as importantly, with the outside world. His rather than in the hardware. But as there were no potential investors around in the aftermath of the Dot.com crisis, that was as far as it went. Four years later, along came a promising fourth-year undergraduate student looking for a project. Ali Dixon took the draft, which included some ideas for the instructions that control the computer, as well as the communications technology and links, and used this to create a model of the processor that could be simulated on a PC.

Dixon came back with fundamental questions about how to write the software that would run on the processors, and so a software tool called a compiler had to be built to take the instructions and convert them into the 1s and 0s that control the processor. This was no simple task as the key to the new architecture was to have lots of small processors all working independently, but running concurrently, which creates a significant problem for traditional software that is essentially designed to be sequential. Moving from this sequential world to one where processors run concurrently required tremendous amounts of research.

XMOS has set out to make the chips itself and build a significant company around the new ideas

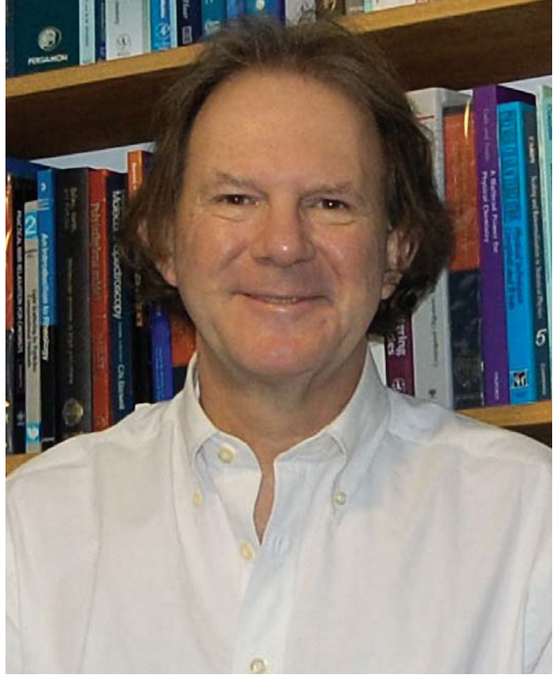
A lot of attention was focused on the ability of the array of processors to handle the input and output of data. "This has been a neglected area over the past 30 years of computer technology, but providing a flexible way for the concurrent software to control data passing in and out of the chip is fundamental to the new architecture," explains May, "and so much of the development was breaking completely new ground". This led to 17 patent applications, covering new ways of handling input and output, memory access and instruction scheduling.

In July 2005, the company XMOS was formed in order to commercially develop the new architecture, now called Xcore, and, in September 2007, XMOS secured $16 million of venture capital funding. The new company has taken the ideas from research, and the investment from the globally renowned venture capital firms, and built a team of experienced and enthusiastic designers and engineers. But instead of just providing the design to other chip makers, XMOS has set out to make the chips itself and build a significant company around the new ideas. "Building the devices is an expensive business and outside the remit and capabilities of the world of research. It has always required new companies to bring together the engineering, business expertise and funding to turn a research idea into reality," says May.

XMOS has taken the concurrent architecture and created the idea of Software Defined Silicon, where the chips provide the performance and low power that usually comes with a hardware implementation, but which can be programmed like any computer, with the input-output and communication between the multiple processors controlled simply through software instructions. The company is now producing a chip with four processor cores that will cost just $10, while a single core version can be even cheaper. There are now two development kits that engineers are using to write all kinds of applications and May wants to see these used in universities to teach computer science and engineering.

The speed at which the company's technology has moved from university science to a commercial proposition has been remarkable. What started as an undergraduate project just five years ago is now a major semiconductor business with plans to revolutionise the consumer electronics market. ■

www.xmos.com



The desire to rid our streets of discarded chewing gum drove Professor Terence Cosgrove in the Department of Chemistry to find a way of preventing gum from sticking to the pavement. Not only will his solution save millions of pounds in cleaning costs for councils around the country, but it has also opened up surprising opportunities for Cosgrove and his team at Revolymer.

Solving a sticky problem

Terence Cosgrove has been working on polymers and their interactions with surfaces for 20 years. Around ten years ago, he was approached by a technology transfer manager looking for a way to remove chewing gum from pavements in order to save councils millions of pounds a year in street cleaning. Nothing came of those discussions, but that led Cosgrove to consider the problem further and five years ago he set up an undergraduate project to investigate it.

The research discovered a polymer that was similar to the polymers used originally in chewing gum (natural rubber). By using a technique called chemical grafting, the polymer was transformed from a hydrophobic material that hates water to a polymeric surfactant that loves it. This enabled the design of a gum that could be easily removed from a range of materials including fabrics, carpets and paving stones. “We found we could easily remove the polymer from different materials but at this stage it was made with toluene, so you wouldn’t want to put it in your mouth,” commented Cosgrove.

Revolymer was created when Cosgrove was introduced to Roger Pettman, a serial entrepreneur with a PhD in organic chemistry. Having created a business plan, the new team entered and won the University’s Enterprise Competition, which led to an initial investment of £750,000 by the IP Group and SULIS, a seed corn investment fund. Over the following year the team, including PhD student Voss Gibson and Dr Erol Hasan, worked out how to make chewing gum. At the same time, they developed a version of the polymer that was safe to use in food and cost-effective for the chewing gum market.

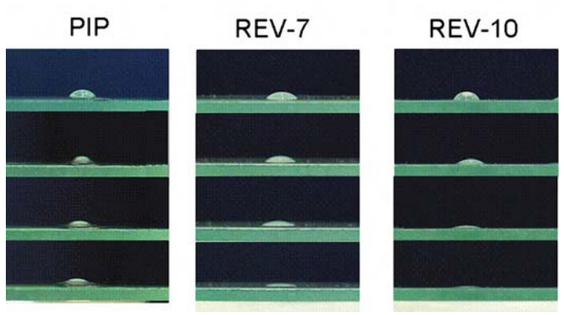
The company filed a series of patents and started making gum in small quantities at the University, initially coming up with over 200 different prototype recipes. “We carried out parallel experiments with commercial gum,” said Cosgrove. “The first ones broke up in the mouth but by optimising the formulations we overcame that, while still maintaining the gum’s disintegration properties. Product development focused on improving the chew, enhancing the initial flavour release, reducing the adhesion and developing a longer-lasting flavour.” At the end of these tests, they had whittled down the gum candidates to four or five variants.

The ‘Big Chew’ took place during Easter 2008. Fifty volunteers from the University and Revolymer chewed their way through 200 samples of gum

It was during this time that the company began to grow and through a strategic alliance with Warwick International, a manufacturer of bleach additives, Revolymer established a research laboratory in Mostyn, North Wales. The agreement was that Warwick would use Revolymer’s polymer coating technology and also manufacture Revolymer’s polymers. A second round of funding provided a further £2 million of investment, plus government grants, which allowed the development of a prototype, but the difficult job of proving the effectiveness of the technology was still ahead. This led to the ‘Big Chew’ event that took place during Easter 2008.

Fifty volunteers from the University and Revolymer chewed their way through 200 samples of gum; some were a commercial brand of gum, some were the Revolymer gum with the polymer additive, and some, acting as control samples, were the Revolymer gum without the polymer. Part of the experiment was to find out how much of the polymer was needed to create the desired effect, so the gum was stuck to the walkway at the Chemistry Department for a month to see what happened. “The results were very exciting. All the gum with our new polymer was easy to remove and this allowed us to choose the best formulation,” said Cosgrove. “Our gum degrades in water and we have subsequently found in real street trials that three out of four cuds will disappear spontaneously with ordinary street cleaning, rain and pedestrian traffic, and the rest should disintegrate with time.”

The company is now in the process of licensing the technology. “You can incorporate the polymer into the gum in various ways, which results in a range of effects,” explained Cosgrove. “The properties vary depending on how cold and wet the environment is, and so you need more additive in a hot, dry country. But we have now established the optimum formulation for use around the world.” The benefits of the new polymers are not confined to gum on pavements: “With the additive it is easy to remove gum from carpets and shoes as well, although it comes off plastic soles more easily than leather ones. We went into the office of the executive of a major investor and stuck gum on his carpet. As we expected, it came off easily, but it was an exciting moment,” he joked.



One commercial (left) and two Revolymer gum cuds. These were all allowed to decay over the same time period.

In May 2008, Revolymer raised a further £10 million towards its goal of commercialising the technology. It is now making the polymer in commercial quantities with a team of 30 people and is selling it to gum manufacturers directly. Food approval is expected in the USA in late 2008 and in the EU in 2009. The polymer technology that has been developed also opens up other markets, including personal care and household products, and drug delivery. With a family of new polymer systems to exploit, Revolymer is much more than just a lifesaver for the gum manufacturers. ■

www.revolymer.com

In May 2008, Revolymer raised a further £10 million towards its goal of commercialising the technology

A vaccine for multiple sclerosis

Apitope Technology Ltd is a biopharmaceutical company that specialises in developing treatments for allergy and autoimmune diseases. Formed as a spin-out company in 2002, Apitope announced in 2007 it had developed a vaccine designed to halt multiple sclerosis in its tracks. Cherry Lewis talked to Professor David Wraith, founder and Chief Scientific Officer, about the vaccine and his struggle to get funding for clinical trials.

David: About ten years ago, Geoff Watts from the BBC came to talk to me about autoimmunity for his *Medicine Now* programme that went out on Radio 4. One of the things we discussed was a new discovery we'd made that was a way of developing vaccines for treating autoimmune diseases and allergies, so-called therapeutic vaccines. They are based on the concept that has been well known for almost a century, namely allergic desensitisation, where people are given injections of the allergen that causes the reaction.

Cherry: Is that the same principle as a vaccine for smallpox?

David: Not really. With the smallpox vaccine, you're giving an attenuated form of the infectious agent which boosts the immune system without actually causing the disease. What we're talking about here are disorders of the immune system which respond to innocuous things such as house dust and pollen that cause an allergy, or proteins in your body that cause autoimmune diseases. In multiple sclerosis, for example, which is an autoimmune disease, the immune system attacks the myelin sheath around nerve cells – the insulating layer that allows the cells to conduct electrical signals. This causes the nerves to function poorly or die and the symptoms of MS to appear. In these 'hypersensitivity' diseases, the immune system is over-responding. We have developed vaccines that can control the immune response, based on the antigens to which the immune system is responding.

Cherry: So how do you activate this desensitisation?

David: There is a set of cells in the body called T-lymphocytes (T cells). Now we know that T cells respond to very small fragments (peptides) of whatever is causing the allergy or the autoimmune disease. We have developed a method of identifying and administering certain peptides so that instead of causing damage, they actually suppress the immune reaction.

Cherry: How very exciting. What happened next?

David: Well, I was talking to Geoff Watts about things and explaining how the biggest challenge we now faced was taking this to the next step, but that it was proving difficult to find funding. Although we have some very large and highly successful venture capital companies in the UK, none of them are funding medical development at an early stage.

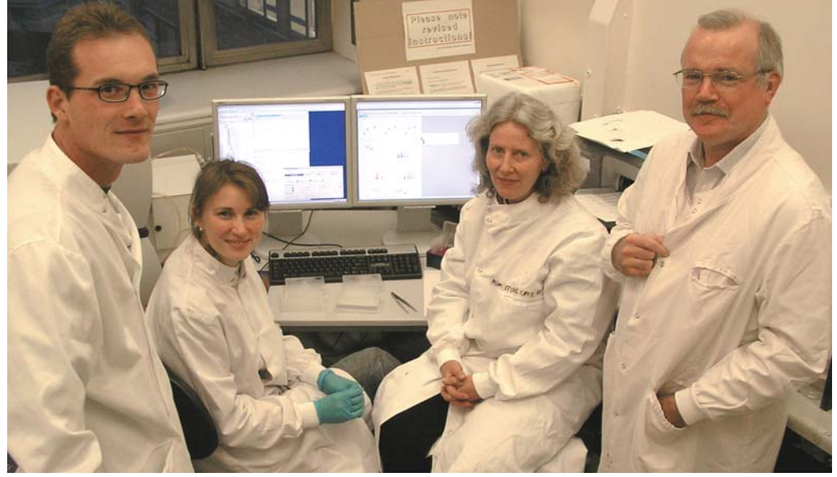
Cherry: What's the reason for that? Is it too high risk?

David: And it's too long term. But what happened to us was very fortunate. An 'angel' investor heard about the programme and offered to help us. He gave us the money to develop our approach to the point where we could take it into clinical trials.

Cherry: That's a powerful argument in favour of talking to the media.

David: Yes, we had a really great discussion and Geoff got very excited about what we had discovered. I'm sure his enthusiasm helped convey the significance of this work. So the business angel provided enough funds for us to develop the vaccine and do what is called 'tox testing' to prove it's safe. You have to prove that the vaccine is not toxic in animals by giving them doses 500 times higher than you would give humans. When this proved successful we were ready to take it to clinical trials, but then we faced another funding hurdle.

For more than two years we discussed funding with the DTI but that eventually fell through for various reasons. I found the whole business incredibly frustrating. Eventually we were awarded a University Translation Award by the Wellcome Trust and that provided close on £1 million for the first clinical trial in humans. This was set up in 2007 under Professor Neil Scolding in the Department of Neurology at Frenchay Hospital here in Bristol. It was what we call a Phase I safety study.



Left to right: Drs Johan Verhagen, Leona Gabrysova and Heather Streeter with Professor David Wraith.

At the end of the trial, one patient even showed remarkable improvement in her eyesight. I think it's fair to say that the trial was highly successful

The aim is to prove that the vaccine can be given safely to humans and there are no adverse effects. Six MS patients at quite an advanced stage of the disease were given our vaccine, memorably called ATX-MS-1467. At the end of the trial, no safety issues had been identified and one patient even showed remarkable improvement in her eyesight. I think it's fair to say that the trial was highly successful.

Cherry: So where are things now?

David: We are now ready to develop the vaccine further and take it to full clinical trials, but we've had to raise a lot more money. Dr Keith Martin, who's the CEO of Apitope, and I have spent the last two years going through endless rounds of talking to funding agencies, venture capital companies, etc, trying to raise the funds, but sadly we haven't been able to raise any funds in the UK. We had various European investors – from Sweden, Germany, Switzerland, France – all willing to join a syndicate to fund our next development. But in order for us to stay in this country, they needed an investor in the UK to take the lead.

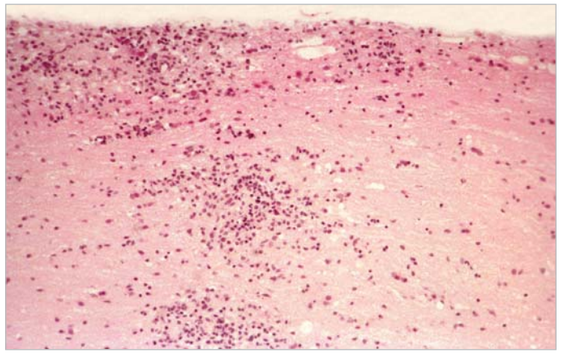
Cherry: And you couldn't find one?

David: We couldn't find one. There isn't a biomedical venture capital company in the UK who doesn't know about us, who hasn't looked at our business plan. Finally we were introduced to a group of Belgium- and Luxembourg-based investors who were very interested and we have just signed a deal with them worth €10 million (£7.7 million). Apitope will now move to Belgium, locating its head office in Diepenbeek, and be called Apitope International NV. The current UK-based Apitope will stay in the UK and become a wholly owned subsidiary of the Belgian company. Among the funders is the University of Hasselt, which will provide support in exchange for an equity stake and will join forces with Apitope by providing its own research on diagnostics.

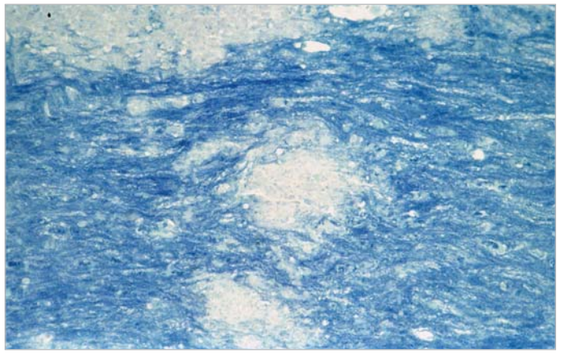
Cherry: How do you feel about that?

David: Our decision to move out of the UK highlights the difficulties UK biotech companies have in raising support, even before the recent financial crisis, especially when it comes to bridging the gap between academic-funded research and advanced clinical studies, where the outcomes are a safer bet. Nevertheless, we have now got the funding so the trials will go ahead and ultimately this will lead to safer and more effective treatments for people with MS. ■

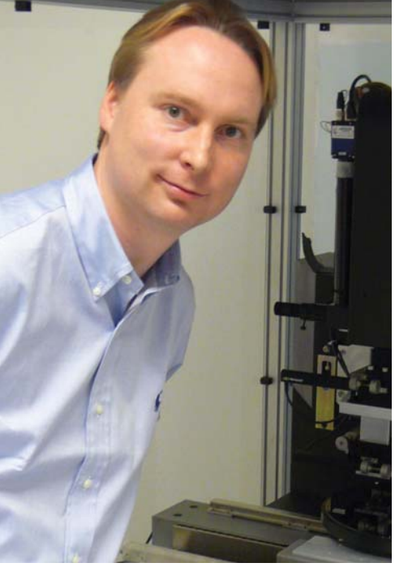
www.apitope.com



The dark cells in this image of a section of the spinal cord are immune cells that have broken through the blood-brain barrier to attack the individual's own tissue. Immune cell infiltration of this type is seen in autoimmune diseases such as multiple sclerosis.



The blue stain shows the myelin sheath that surrounds nerve axons in the white matter of the brain and spinal cord. This image reveals the demyelination caused by the immune cells shown in the adjacent image. Myelin loss such as this is commonly observed in diseases such as multiple sclerosis.



Dr Andrew Humphris

Examining the infinitesimal

A new approach to microscopy is opening up the wonders of the molecular world, allowing researchers to examine organic molecules and delicate crystals as they grow, atom by atom. Dr Andrew Humhpris, co-founder of the original technology and now Chief Technology Officer of Infinitesima, explains how this University spin-out has turned into a leading-edge company.

The smallest bacteria are around 200 nanometres in length; a DNA double helix has a diameter of around two nanometres; and the space between two carbon atoms is only 0.15 nanometres. To put these numbers in context, one nanometre is one billionth of a metre, or the size of a marble when a metre represents the size of the Earth. In other words, incredibly small. With nanotechnology becoming increasingly important in a whole range of scientific fields, being able to see things at higher and higher magnifications is crucial.

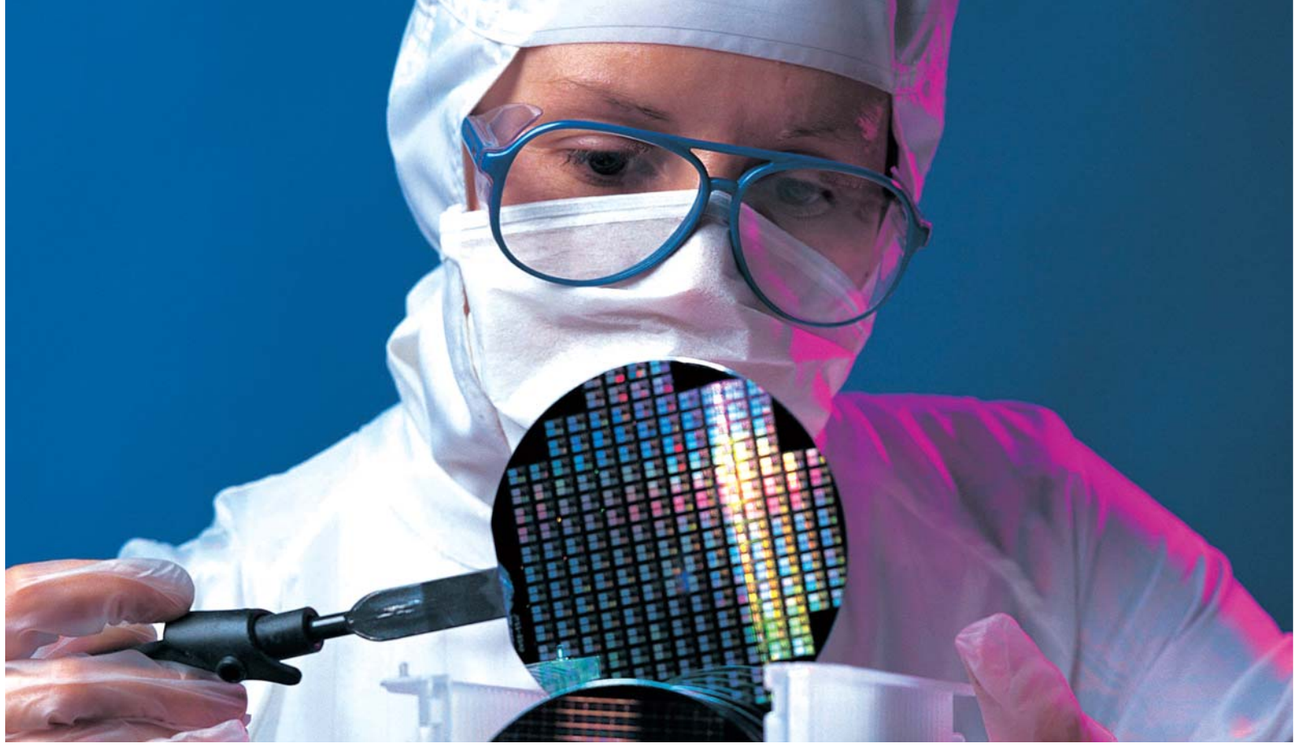
There are several ways of looking at materials at the atomic and molecular scale but many, such as scanning electron microscopes, only work in high-vacuum chambers. This can be cumbersome when loading and unloading samples, which also need to be electrically conductive. A different approach is atomic force microscopy (AFM), although the term 'microscopy' is something of a misnomer, because this microscope does not really 'see' anything. Information is actually gathered by 'feeling' the surface of a sample with a probe, much like the needle of a record player moves over the surface of a record. The advantage of AFM is that the sample does not need to be in a vacuum, so live biological material can be examined. Consequently, AFM has been widely used over the past 20 years to move atoms around and even spell out words using individual atoms, but there are still two major drawbacks: the technique is very slow and it cannot be used for very delicate samples, because it damages them in the process.

Professor Mervyn Miles

Professor Mervyn Miles, Head of the Nanophysics Group in the Physics Department, and his team took these challenges to heart and resolved to change the way AFM systems were designed, but instead of trying to make the probe smaller, they looked at ways to make the measurements faster by increasing the probe's sensitivity. Using new combinations of materials with which to build the probe, they first managed to reduce the time it took to generate an image from several minutes to just 50 microseconds, thereby enabling the AFM to produce a series of stills that is, in effect, a video of the sample. A key benefit of this approach is that it allows highly delicate samples to be examined, without destroying them in the process. This sensitivity, combined with the video capability, allows biological samples to be examined as they move and crystals to be watched as they grow, atom by atom, revealing a whole new molecular world.

The advantage of atomic force microscopy is that the sample does not need to be in a vacuum, so live biological material can be examined

In 2001, the success of this research led to the launch of a spin-out company called Infinitesima in order to develop novel instrumentation and components for existing AFM systems. Instruments were sold to research groups around the world that are pushing back the boundaries of our understanding of molecular activities and by 2004 the company had moved to its current location in Oxford. In 2006, Infinitesima was selected by *Real Business* magazine as one of the '50 to Watch' start-up companies in the UK. The selection was recognition of the technology, now called Resonant Probe Microscopy (RPM), that Infinitesima brings to the nanotechnology sector.



Inspecting a silicon wafer.

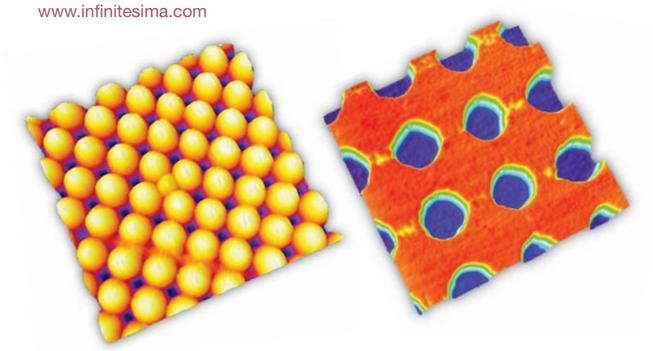
Infinitesima now supplies several products based on RPM, including VideoAFM which is capable of observing processes and delivering real-time images at unprecedented rates, enabling large areas of sample to be explored. The microscope probe measures just 100 microns across and is made of silicon or silicon nitride, depending on the type of sample being measured. The instrument delivers real-time video at the molecular level, allowing researchers to operate the apparatus much like an optical microscope, but at staggeringly higher magnifications. A technical advisory board, chaired by Professor Mervyn Miles, is made up of leading scientists and researchers in the field who advise the company on its technological development. Today, Infinitesima has a growing number of staff, including a highly experienced management team, and backing from private investors to take the company forward into new areas.

VideoAFM delivers real-time video at the molecular level and can be operated much like an optical microscope

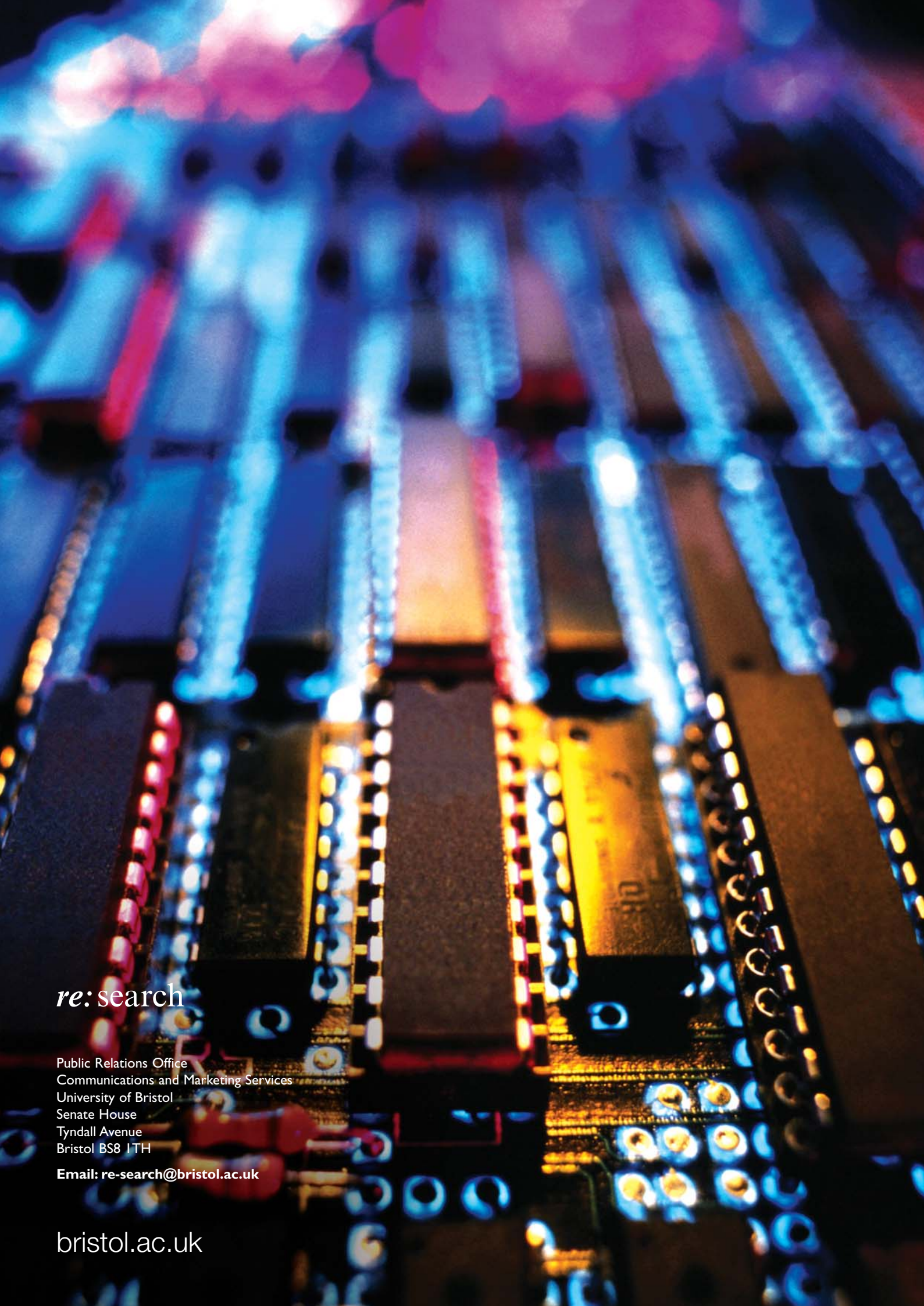
Silicon wafers, for example, need to be inspected closely and quickly for defects, ideally as part of the production line, but current techniques are too slow and require the wafer to be in a vacuum, which is possible but cumbersome. With high-speed atomic-scale imaging in air, wafers can be examined directly to see whether there are any process defects or tiny particles on it – the equivalent of identifying and taking a picture of a single blade of grass in a football pitch. Another area that has recently opened up is in the processing of semiconductors, where a single atom difference in thickness at certain points can dramatically alter the performance of some devices. Being able to examine atoms directly is therefore of tremendous value. But rather than video, the semiconductor processing industry needs fast, single pictures which the RPM process is able to provide. RPM is therefore being incorporated into semiconductor processing tools to provide these images on high-throughput, continuous production flows. The first of such products from Infinitesima for this large, established industry was introduced in October 2008.

Beyond the semiconductor market, manufacturing of devices of all types is moving towards the nanoscale. From automotive sensors to mobile phone microphones to digital camera lenses, miniaturisation has progressed to the point where nanoscale inspection techniques are required to 'see' what is being produced and Infinitesima is poised to benefit from this rapidly shrinking world. ■

www.infinitesima.com



Left: An array of 100 nanometre aluminium bumps on the surface of glass.
Right: Holes in a silicon oxide layer, just 400 nanometres in diameter.
Each image collected in under a second using Infinitesima's RPM technology.



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