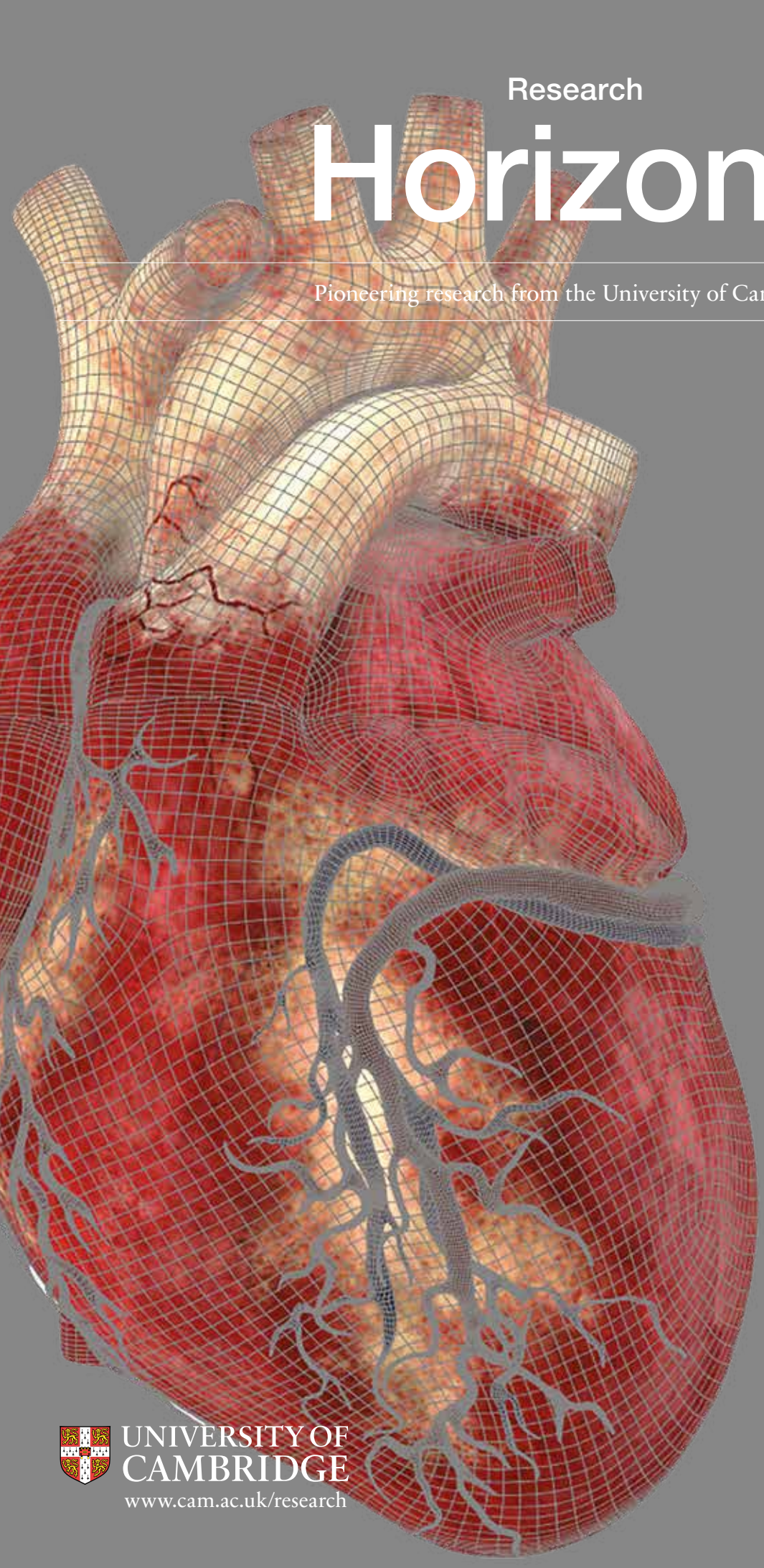
Research

Horizons

Pioneering research from the University of Cambridge



Issue 33

Spotlight

Future therapeutics

Feature

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UNIVERSITY OF CAMBRIDGE

www.cam.ac.uk/research

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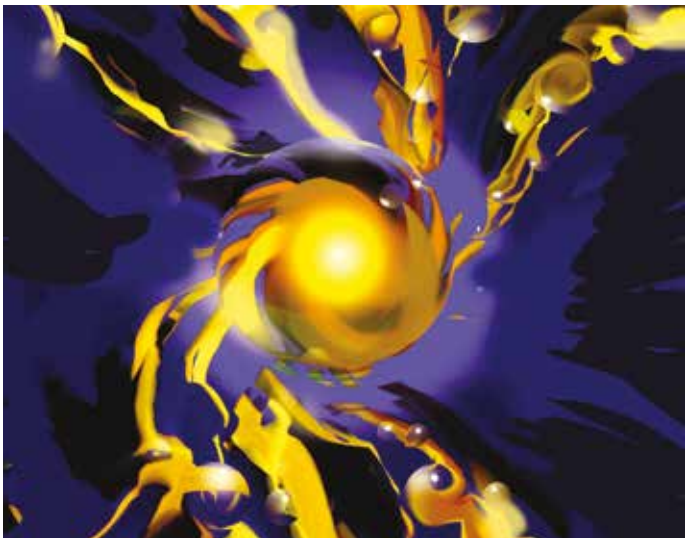

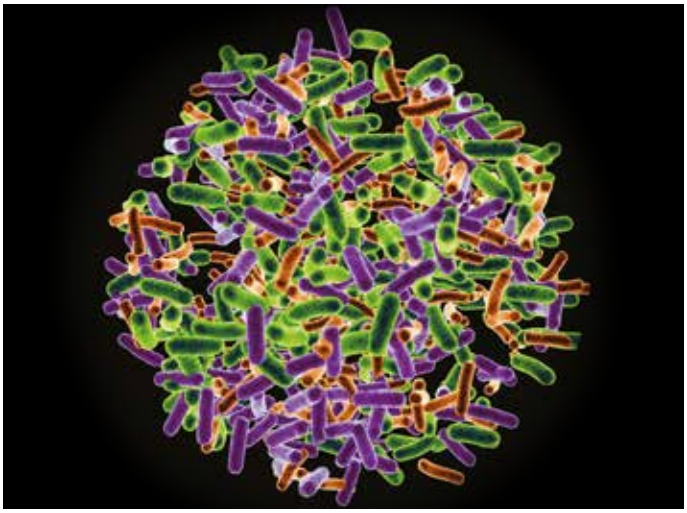

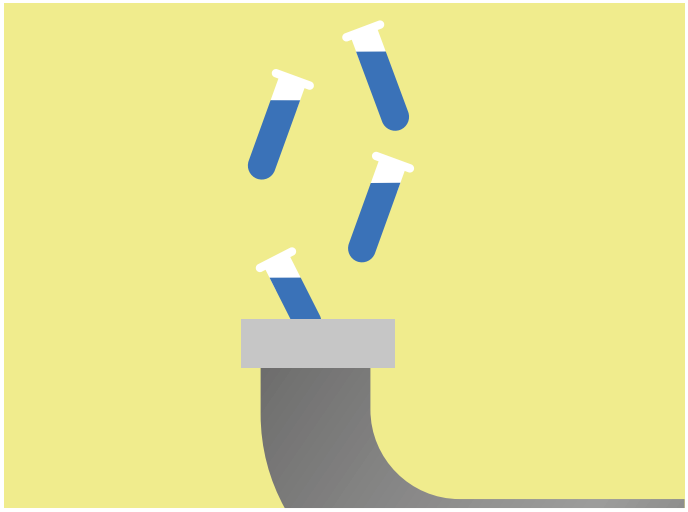

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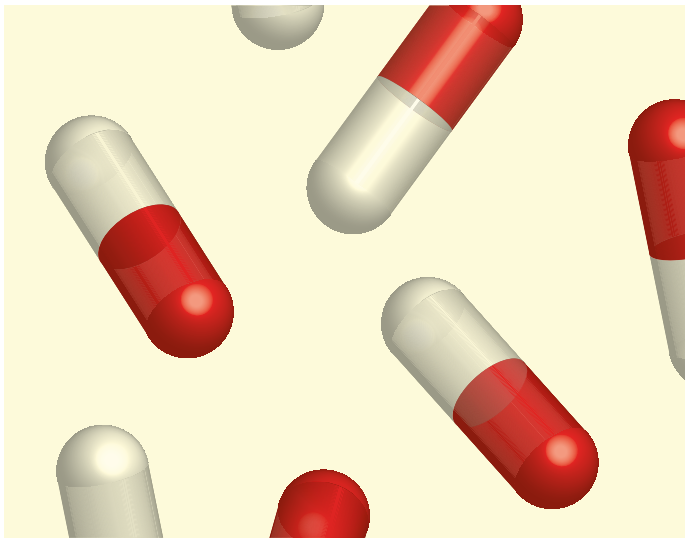

Welcome

Nanobots small enough to move around our bloodstream, damaged hearts repaired with 'off-the-shelf' pieces of beating tissue, genetic diseases cured by 'molecular scissors' that snip out and replace faulty DNA. These coming innovations – and many more – have the potential to change the face of therapeutic medicine.

Meanwhile, a step change is happening in the pipeline from Petri dish to pill. Major efforts are being directed at strengthening the collaboration between academia and industry at several stages of the drug development process to reduce the high rates of drug failure in clinical trials.

This issue of *Research Horizons* covers some of these discoveries and developments happening right now in Cambridge. It comes at an exciting time, as the Cambridge Biomedical Campus continues to flourish and grow. It also coincides with the launch of the Cambridge Academy of Therapeutic Sciences – an initiative that aims to forge new links between academic research, biotech, big pharma and the NHS, to help smooth the translation of fundamental and applied research into patient treatments.

Elsewhere in the issue we cover ground-breaking work on pregnancy at our Centre for Trophoblast Research and at the Barcroft Centre, a newly opened sister research facility. We also shed light on the networks behind people smuggling in Europe, and hear about a political leader's manoeuvring to make his nation "great again". We learn how electron 'spin' could hold the key to managing the world's growing data demands, and we discover why we should eat millet with everything.

Finally, in our *Things* article, you'll find an assortment of items from our museums, archives, library and botanic garden connected by India. We've made a short series of films to tell each of their stories as part of India Unboxed, a year-long celebration across Cambridge to mark the UK–India Year of Culture.

We hope you enjoy this issue.

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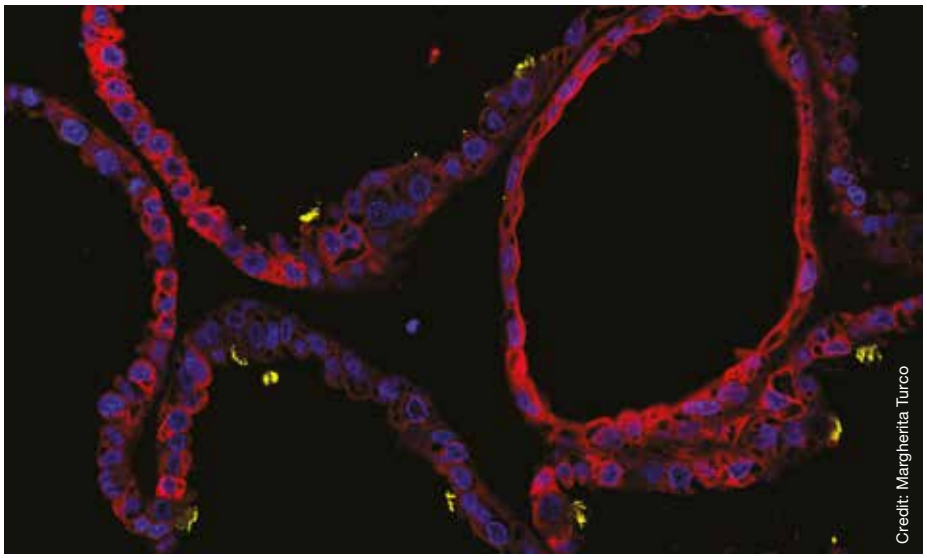
News



Miniature 'womb lining' grown in lab

'Womb organoids' could provide new insights into the early stages of pregnancy.

A team from Cambridge's Centre for Trophoblast Research (CTR) has for the first time grown human tissues that function like the lining of the womb (the endometrium). The cells respond to female sex hormones and early pregnancy signals, and secrete 'uterine milk' proteins that nourish and stimulate the embryo during the first few months of pregnancy.

The researchers believe it's a major step forward in investigating the changes that occur during the menstrual cycle and when the placenta is established. "These events are impossible to capture in a woman, so until now we have had to rely on animal studies," says lead researcher Dr Margherita Turco.

"Events in early pregnancy lay the foundations for a successful birth, and our new technique should provide a window into these events," adds Professor Graham Burton, Director of the CTR. "There's increasing evidence that complications of pregnancy, such as restricted growth of the fetus, stillbirth and pre-eclampsia – which appear later in pregnancy – have their origins around the time of implantation, when the placenta begins to develop."

Image
Organoid grown from human endometrial cells

The work adds to a series of 'firsts' at the CTR, which this year celebrates its tenth anniversary. Other successes include filming development of the human embryo beyond the stage it implants into the womb, demonstrating the mechanism that links lack of oxygen in early life to cardiac and vascular disease in later life (see p. 14), and showing that adverse immunological interactions between the mother and fetus are associated with miscarriage and pre-eclampsia.

Turco, Burton and colleagues are now confident that their new advance will provide a much-needed window on events during the earliest stages of pregnancy, when the conceptus and mother interact physically for the first time.

www.trophoblast.cam.ac.uk

Data-driven discovery

New supercomputer to help answer questions that were previously too complex to even pose.

Analysis of vast datasets of everything from turbulence simulations for the aeronautical industry to real-time analytics for use in hospital decision-support systems will be faster thanks to a new high performance computing facility in Cambridge.

The service will use an innovative petascale high performance computing platform and is expected to unlock breakthroughs in a broad range of disciplines.

"Today, leading-edge science, technology, medicine and commerce in Cambridge and across the UK create huge amounts of data. There is more demand for high performance computing to analyse large-scale datasets than capacity, creating a bottleneck that thwarts progress," explains Dr Paul Calleja, Director of High Performance Computing Services at the University.

"Not only will our facility work extremely fast, boosting our national capability and reducing the wait for access to high performance computing, it provides a new order of processing. Those doing ground-breaking work will use our service to answer questions that they are unable to even pose to the current facilities, and that is really exciting."

Cambridge's Research Computing Service, the Engineering and Physical Sciences Research Council (EPSRC) and the Science and Technology Facilities Council have provided £14.6m to create the Cambridge Service for Data Driven Discovery.

The EPSRC element of the service is a consortium led by the University of Cambridge in partnership with the Universities of Bristol, Leicester, Southampton and Oxford, King's College London, University College London and Imperial College London.

News in brief

More information at www.cam.ac.uk/research

24.04.17

Researchers show that commercially bred caterpillars are able to eat shopping bags, suggesting a biodegradable solution to plastic pollution.

20.04.17

Cambridge is one of five centres that will form the UK Dementia Research Institute, which aims to diagnose, treat and prevent dementia.

Major investment to improve healthcare

Cambridge awarded £40m to create a world-leading healthcare improvement research institute.

A new institute to be based at the Cambridge Biomedical Campus will strengthen the evidence-base for how to improve healthcare, as well as help the NHS to become the world's largest producer of systematic learning in this area.

The institute's researchers will work with NHS staff, patients and carers to identify, design and test proposed improvements on a much wider scale than is currently possible. It will also fund a world-class fellowship programme open to applications from UK universities to build skills in improvement research across the UK, creating a new, highly skilled generation of researchers.

"The NHS, like health systems around the world, is faced with pressing challenges of quality and safety," explains Professor Mary Dixon-Woods, the institute's inaugural Director. "But, the science of how to make improvements has remained underdeveloped. This award is a tremendous opportunity to produce new knowledge about how to improve care, experience and outcomes for patients."

Funded in the region of £40m over ten years by the Health Foundation, an independent charity, the institute will work closely with RAND Europe, Homerton College Cambridge and other partners in the health service, university and charity sectors across the UK.

Credit: Cambridge University Library

Discarded history: the Genizah of Cairo

The world's most important collection of medieval Jewish manuscripts – chronicling 1,000 years of history – have gone on display.

From the 9th to the 19th century, the Jewish community of Old Cairo deposited unwanted writings in a purpose-built storeroom in the Ben Ezra synagogue. The texts were considered too holy to throw out because each contained the name of God.

But when the 'Genizah' room was opened in the late 19th century, alongside the expected Bibles and prayer books, scholars discovered documents of everyday life: shopping lists, marriage contracts, works of Muslim philosophy, business letters, medical books and a 1,000-year-old page of children's doodles. Practically every kind of written text had been preserved.

"This colossal haul of writings reveals an intimate portrait of life in a Jewish community that was international in outlook, multicultural in make-up and devout to its core; a community concerned with the very things to which humanity has looked for much of its existence: love, sex and marriage, money and business, and ultimately death," explains Dr Ben Outhwaite, Head of the Genizah Research Unit and co-curator of an exhibition of the manuscripts at Cambridge University Library.

The treasures were discovered in 1896 by twin sisters Agnes Lewis and Margaret Gibson, who passed the information to Cambridge lecturer Solomon Schechter. Upon Schechter's arrival in Cairo, the Chief Rabbi of Egypt gave him permission to take whatever he liked. Schechter declared that he "liked all", and shipped almost 200,000 manuscripts back to Cambridge.

"We have translated most of these texts into English for the first time – and most are also going on display for the first time," adds Outhwaite. "We hope to make this medieval society accessible and recognisable to a modern audience."

Image
Solomon Schechter and the manuscripts in 1898

Film available:
http://bit.ly/2oLEccH

28.03.17

'Big data' research study finds that encouragement from teachers has the greatest influence on less-advantaged children.

07.03.17

An incomplete and largely forgotten Italian opera by Franz Liszt is resurrected, completed and given its world premiere.

23.02.17

£10m funding for advanced materials research to improve energy storage technologies and develop energy-efficient devices.

TRADING ON HUMAN TIDES

Words
Fred Lewsey

Cambridge criminologists are using emerging sources of information – from court records to Facebook groups – to analyse the networks behind one of the fastest-growing black markets on the planet: the smuggling of people into Europe.

A wiretapped telephone records a human smuggler in Sudan asking a human smuggler in Libya how many were his. The response is 109, of whom 68 are now dead.

The boat had capsized within sight of the Italian island of Lampedusa, killing 366 people. At the time, autumn 2013, it was the single largest loss of life to result from the booming black market in Mediterranean crossings. Worse would follow.

The wiretap later records the smuggler in Sudan reproaching the smuggler in Libya for overcrowding the boat. The smuggler has since felt obliged to personally notify families. He has shelled out $5,000 in compensation in a bid to save his reputation and stop potential customers turning to one of his many rivals.

Human smuggling is different to human trafficking: the smugglers' commodity is the crossing of borders rather than control over people – and war, poverty and globalisation have caused demand for this commodity to explode.

Between 2014 and 2015, illegal border crossings along the East Mediterranean route increased by an astonishing 1,641%: from around 50,000 to over 885,000. As with any market, let alone one of the fastest growing on the planet, where fortunes are to be made competition is ferocious.

Dr Paolo Campana, an expert in criminal networks, joined Cambridge's Institute of Criminology in early 2015. He describes the commerce of smuggling humans into Europe as a "quintessential free market", with little intervention and no regulation beyond the market's own mechanisms.

"Some smugglers cheat, some overcharge, some care about safety, some don't care who lives or dies. Some offer 'premium' services, fast-tracking migrants through smuggling routes. Some don't protect people from kidnappers, others help buy them back from militias," he says.

"The law struggles to apprehend smugglers, and when they do manage it, any void created is likely to be immediately filled. The main things that stop smugglers defrauding many more migrants, or drowning them in unseaworthy boats, are individual morality and maintaining a reputation that attracts more business."

Importantly for a pure free market such as human smuggling, there are no monopolies, says Campana. While newspaper headlines will often describe 'Mr Big' figures or talk of Mafia involvement, his research shows that smuggling networks are fragmented: small groups with rudimentary hierarchies jostling for trade in crowded marketplaces.

"Despite smuggling routes traversing the globe, from the Horn of Africa to Scandinavia, individual operations are stunted and localised – nobody is in control of all stages of the journey. Smugglers operate as independent actors in various stages of an overall journey, whether it's a sea or a desert crossing, or temporary city accommodation, or car trips over European borders."

"While some smuggling groups make arrangements with each other, there seem to be no exclusivity agreements and – despite the localisation of smuggling networks – very little territorial control," says Campana.

This absence of monopolies is radically different to other black markets such as Mafia-like protection

rackets. Even in Sicily, where both human smuggling and the Mafia are major problems, Campana observed no connection between the two.

Almost anyone can set themselves up as a smuggler: from street vendors who sell border crossings as a sideline, to tour guides who switch to smuggling, to fishermen who are already equipped with boats for the sea crossings. It is the free-for-all nature of this marketplace that gives it the flexibility to expand quickly and accommodate soaring demand.

"Human smuggling is an enterprise with low barriers to entry, low skills and relatively low capital requirements – yet it has the potential to be far more lucrative than most other occupations available to people on the smuggling routes."

As one operational analyst from the European border agency Frontex told Campana: "If you carry 20 people in a boat, that could be the equivalent of five years' bad fishing."

In the wake of the 2013 Lampedusa shipwreck, a rescue operation, initially called Operation Mare Nostrum, was set up to patrol the Mediterranean, and resources from the highly skilled anti-Mafia prosecution unit in Palermo were allocated to tracking human smuggling operations for the first time.

Campana combed through and coded the smuggling court cases and wiretapped evidence that resulted from this shift, and has created quantitative databases to model smuggling networks.

As well as interviewing the Frontex analysts in Warsaw, he has also travelled to small towns in Greece and some of the Italian islands to speak to migrants, the police and the local communities.

He has just started to publish the findings from this research, including an overview of the new smuggling markets. He hopes that the first quantitative network analysis of a human smuggling operation – the one involved in the Lampedusa disaster – will also be public later this year.

Campana is also working with his Institute of Criminology colleague Professor Loraine Gelsthorpe, who has worked for many years with victims of trafficking, to conduct further interviews to capture the voices and experiences of migrants and smugglers. Gelsthorpe is co-founder of the Cambridge Migration Research Network, CAMMIGRES, which aims to improve understanding of migration.

"Professor Gelsthorpe and I are taking a genuinely holistic approach by combining the data-driven with the experiential," says Campana.

One of the key areas the researchers are exploring is how migrants choose who to trust in such a busy and dangerous marketplace. This comes back to reputation.

While some smuggling networks are organised around ethnic lines, and word of mouth is important, digital forums have become increasingly influential in establishing trustworthiness, so part of the research involves analysing social media.

Smugglers often advertise their services in Facebook groups, where they try to attract 'customers' by responding to queries, competing through prices, and promoting credentials in the form of recommendations from other migrants.

Payment happens in advance, often through *hawala*, a traditional honour system that now functions through text messaging and a vast network of brokers. In some ways these platforms and processes are not that different to using eBay, for example, but with far more at stake.

Online networks are particularly significant in Syrian communities, where there is on average a higher level of education and digital literacy. "As everywhere, education matters," says Campana. "Accessing and evaluating information through channels such as Facebook could mean the difference between life and death."

Campana's research has led him to question the European Union's focus on policing and naval operations in the Mediterranean to control human smuggling. "Naval operations are very noble; however, they have the unintended consequence of assisting the smugglers by taking the refugees off their hands very close to the Libyan coast – making the 'product' more attractive and, ultimately, increasing the number of journeys.

"This is a market driven by exponential demand, and it is that demand which should be targeted. Land-based policies such as refugee resettlement schemes are politically difficult, but might ultimately prove more fruitful in stemming the smuggling tide."

www.cammigres.group.cam.ac.uk

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Credit: Mstyslav Chernov/Unframe

Egg & bacon
Egg, sausage & bacon
Egg & millet
Egg, bacon & millet
Egg, bacon, sausage & millet
Millet, bacon, sausage & millet
Millet, egg, millet, millet, bacon & millet
Millet, millet, millet, egg & millet
Millet, millet, millet, millet, millet, millet, b
Lobster Thermidor aux crevettes with a M
brandy and a fried egg on top, & millet.*

Archaeological research shows that our prehistoric ancestors built resilience into their food supply. Now archaeologists say 'forgotten' millet – a cereal familiar today as birdseed – has a role to play in modern crop diversity and in helping to feed the world's population.

Over half of the food consumed by the human race in terms of calories comes from just three species of grain – wheat, rice and maize – yet in biological terms all are highly unnatural. They've been bred, generation after generation, to have grains that are super-sized in relation to their stems. This is perfect for maximising crop yields and profits, but not so perfect if growing conditions change in a changing climate.

Professor Martin Jones, Head of Cambridge's Department of Archaeology and Anthropology, is far more interested in a group of around 20 species of small-grained cereals that are generically termed millets. They look like wild grasses, don't need much water, grow quickly and have a good nutritional balance. Yet, until recently, they have been largely overlooked by the Western world as a food source for humans, and are most commonly found in packets of birdseed.

Now Jones has brought attention to this ancient grain as a means of mitigating against the boom–bust nature of harvests. His work has contributed to a growing market in Asia for high-quality millet from Aohan, Inner Mongolia, and the cereal's potential is attracting interest from big multinational companies.

All of this has come from Jones' archaeological interest in ancient farming practices. Searching for evidence of millet in the Neolithic, he discovered two key species – broomcorn and foxtail millet – in the prehistoric crop record in Europe, despite both being botanically East Asian. By piecing together the archaeological evidence, it became clear that Asian millets were coming into Europe, and that wheat and barley from Europe were moving into Asia.

"This wasn't a time when farming was transitioning from hunter-gathering to agriculture," says Jones. "What we were seeing was a move from single-season, single-crop agriculture to multi-season, multi-crop agriculture." Hundreds of years ago the Asian millets were being used in flexible and innovative ways, and became among the most geographically widespread crops in the world. By using crops from other regions, the farmers could add another growing season and significantly increase their yields.

Jones' archaeological work took him to a new site in Aohan when evidence emerged of local millet cultivation in Neolithic times. There, his Chinese colleagues found carbonised particles of foxtail and broomcorn millet dating from 7,700 to 8,000 years ago, which proved to be the earliest record of their cultivation in the world.

But it was his conversations with local farmers that radically altered his perception of the grains. "When we first visited Aohan it could sometimes be hard to tell whether the millet was growing as a crop or as a weed. We asked the locals, and rather than tell us it was a stupid question – that it was irrelevant whether it was crop or weed – they politely answered a different one. They told us what it tasted like and when they last ate it. These people had lived through hard times, famines, so to survive they had developed more open ideas. I realised then that I'd come with concepts that seemed universal but just weren't relevant to the lives of people in contemporary northern China."

The development of their farming practices, like those of the ancient farmers, was driven by the need for resilient plants that could ripen to harvest in challenging years, to ensure food security for the population. "What archaeologists can't reconstruct is how much the early farmers understood the significance of what they were doing," says Jones, "but this – and what we've heard from today's Aohan peasant farmers

Millet with everything.

Words
Jacqueline Garget

aked beans, millet, millet, millet & millet Mornay sauce, garnished with truffle pâté,

– is something we can learn from in addressing our current food challenges."

"With harvests and growing conditions intimately linked, the changes in climate now happening across the world pose a real threat to food security in certain regions," adds Jones. "To get the unusually big grain size we see in wheat, rice and maize, a lot of the properties that give the plants inherent resilience have been sacrificed. Being geared towards producing heads of large grains is terrific if you can guarantee all the water, nutrients and sunlight they need. But the crops are much more prone to complete failure if something changes, like the amount of rainfall in a growing season. It's like putting all your eggs in one basket."

For farming systems where there's no financial infrastructure providing subsidies and grants to help farmers control the growing conditions through irrigation, pesticides and other methods, inherent crop resilience can be vital to a successful harvest.

"Millets have an unparalleled genetic diversity both because of their long history of cultivation, and because they've been grown in so many regions of the world, including very harsh ones," says Jones. "This means they've retained the wild traits that give them resilience to changes in growing conditions. They don't need much water, they grow quickly, and they have a great nutritional balance."

After his work demonstrated the importance of the Asian millets and their origins in northern China, the Food and Agriculture Organization of the United Nations recognised the Aohan Dryland Farming System as a 'Globally Important Agricultural Heritage Systems' site. Aohan millet is now badged as a high-quality product and sold in large quantities to the domestic Chinese market, where it is a staple food. This year, Jones was among those awarded a medal from the Aohan government, not only for raising the profile of Aohan millet but also for helping the farmers to turn around the fate of this once overlooked crop, with support from their local government.

"I'm delighted that the Aohan government found such a useful and practical connection to academic research," says Jones. "For me, talking to the farmers and local people in Inner Mongolia has taught me that their knowledge about plants is enormous."

Given the increasing number of extreme weather events, and a growing population demanding a more varied diet, the world is facing a potential crisis in terms of food security. Aid agencies in Africa are becoming more aware of the practice of growing millet alongside the central maize crop as a safeguard against total harvest failure and are supporting farmers in Africa to continue to do this. And UK producers are showing interest in millet as a raw ingredient in branded consumer foods to help people improve their health and wellbeing.

"A huge amount of research linked to food security has focused on the really major crops," says Jones. "Millets have taught me that it's worth shifting the focus. We may have a lot still to learn from our Neolithic predecessors."

Research funded by the European Research Council, the Natural Environment Research Council, the Wellcome Trust and the Leverhulme Trust.

* With thanks to Monty Python's *Spam* sketch.

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MAKE ROME GREAT AGAIN

Fake Views in the Ancient World

A political leader who seeks to make his nation "great again" and a time when 'post-truth' rhetoric appears to support political ambitions. Not Trump's America, but Rome 2,000 years ago.

The elusive, glorious past has been a dominant theme of recent political slogans and soundbites. President Trump's rallying call to "make America great again" was met with outpourings of support on his campaign trail and, in the wake of the EU referendum, British politicians have referred to our history as a great global nation, saying that Brexit offers the opportunity to retake our place as a great world power.

The tactic of alluding to an idealised point in the past, embodying all of a country's best values, while glossing over times of hardship, is nothing new. In fact it's as old as the hills, and at least as old as the seven hills of Ancient Rome.

The first imperial regime of Rome started in 27 BC after a long period of civil unrest and brutal bloodshed. After Octavian defeated his rivals for power, Antony and Cleopatra, he cleverly rebranded himself as Augustus and began what would become a monarchic regime. He disguised this new order as the continuation and restoration of the Roman Republic and recast the historical and cultural memory of Rome to suit his own needs of self-preservation and self-promotion.

Dr Elena Giusti, in the Faculty of Classics, is working on a book examining the part that the *Aeneid,* written by Roman poet Virgil, played in shaping the narrative of Emperor Augustus' regime. Her book will contribute to a long-standing academic debate over the extent to which the poem is propagandistic.

"My interest in Augustan poetry and its tendency to reshape traditions and place facts in a position of secondary, subsidiary importance was inspired by my experiences as a millennial growing up in Berlusconi's Italy," says Giusti. "My research focuses on what, after the events of 2016, we might dub 'post-truth poetics' – and a reading of Virgil's *Aeneid* as a form of poetics and politics that aimed to shape public opinion by appealing to feelings rather than facts."

Virgil's epic poem tells the story of Aeneas the Trojan hero and his struggle to found the Roman race. In Giusti's view, Virgil was in all likelihood commissioned by Augustus to write the *Aeneid*, and there is certainly plenty to suggest that he wrote his epic work in compliance with the new regime.

Giusti's research explores Virgil's exploitation of one historical period in particular, the age of the Punic Wars from 264 BC to 146 BC. This long-running conflict was fought between the Roman Republic and Carthage, an ancient city located on the coast of modern Tunisia.

In alluding to the Wars, from which Rome emerged victorious, Virgil transports the reader back to a "mytho-historic" time of strength and glory in Rome's past. The real threat from Carthage ended after the defeat of Hannibal in 201 BC, but Virgil uses Carthage to evoke *metus hostilis* or 'fear of the enemy'. The poem aims to unite the Romans, shaken by the trauma of recent civil conflict, by reminding them of a time when the greatest threat was from a foreign power.

"Civil conflict had brought Rome to its knees, and the use of Carthage in the poem appears to suit the ideological needs of foregrounding foreign conflict while whitewashing the reality of the strife against fellow citizens on which the principate itself was built," explains Giusti.

In the *Aeneid*, Virgil presents Carthage through a thick layer of mythical and historical allusion, blending historical events and points in time to suit his political purpose. The blurred spatial and temporal narrative allows Virgil to mingle not only Ancient Greek mythology and the Punic Wars, but also the more recent historical events of the civil war, by making

The tactic of alluding to an idealised point in the past, while glossing over times of hardship, is nothing new. In fact it's as old as the hills, and at least as old as the seven hills of Ancient Rome

Words
Shelley Hughes

Credit: Till Niermann on Wikimedia

clear allusions to the history of Antony and Cleopatra in the relationship between Aeneas and Dido, Queen of Carthage.

Virgil conjured a series of associations between the Punic Wars and recent Roman civil disorder. The effect was to ascribe to the latter the qualities of foreign conflict and interference by an external enemy. This fictional history, where it was the destruction of Carthage that brought about the crisis of the Republic, served to legitimise Augustus' involvement in the civil war and vindicate him of any wrong-doing.

On the face of it, then, Virgil's 'post-truth poetics' appear to overwhelmingly support the ambitions of Emperor Augustus to 'make Rome great again'. However, Giusti also thinks that Virgil's epic ultimately exposes the illusory nature of Augustan Rome and the suggestion that the new imperial order was founded in the wake of foreign rather than civil wars, which any learned reader in Rome at the time would have known to be 'post-truth'.

Just as a modern-day political speechwriter charged with harking back to the past with romanticised stories of empire might be required to suppress their better judgement and awareness of historical fact, Virgil appears to have negotiated a vision of the Punic Wars that he himself realised was little more than a nostalgic mirage.

Giusti argues that when Virgil starts to make Carthage look like Rome, and the Carthaginians like Romans, rather than the foreign enemy, memories of the recent civil wars are brought to the surface. Paradoxically, Virgil's Carthage unveils the delusory nature of Augustus' restoration of the Roman Republic and its mythical history. The artificiality of the image that Virgil conjures stimulates us to interrogate the legitimacy of the stories and messages encoded in the narrative.

Perhaps this indicates the author's frustration at writing in support of the Augustan regime. "We know that Virgil, like most Romans, suffered personally during the civil wars and that his family's property was confiscated, although subsequently restored. To me it is clear from the poem that his primary historical concern was actually the traumatic memory of the civil wars and the subsequent subversion of Rome's Republican institutions," adds Giusti.

Perhaps this image of an author conflicted in his work serves to explain why, according to legend, Virgil tried to have the *Aeneid* destroyed before he died. He was prevented from doing so by Augustus and his vision of "empire without end".

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Words
Tom Kirk

THE ELECTRON MANIFESTO

Electron 'spin' could hold the key to managing the world's growing data demands without consuming huge amounts of energy. Now, researchers have shown that energy-efficient superconductors can power devices designed to achieve this. What once seemed an impossible marriage of superconductivity and spin may be about to transform high performance computing.

In the early days of the computer, calculators were room-sized and public demand was low. Now, it's the reverse. Digital technology has become smaller and faster, and our dependence on it has grown.

We are almost desensitised to a stream of facts about the startling rate at which this is occurring. In 2016, IBM found that humans now create 2.5 quintillion bytes of data daily. From the start of this decade to its end, the world's data will increase 50 times over.

The basic building blocks of electronic devices, such as the transistor, work by moving packets of charge around a circuit. A single unit of charge is an electron, and its movement is governed by semiconductors, commonly made from silicon. But technology based on these principles is now reaching a point where it cannot get much smaller or faster. A paradigm shift is due.

"There have been many failed attempts to oust silicon from its predominance," reflects Professor Mark Blamire, Head of Materials Science at Cambridge. "Something has to be done because the technology can't be scaled to smaller sizes for very much longer. It's already a major source of power consumption. There's no obvious competitor, so in a sense the opportunity is there."

Blamire and his colleague Dr Jason Robinson are leading several major programmes investigating one such competitor, known as superconducting spintronics.

> **"We aren't just trying to do something better; we are offering something entirely different and new"**

The launch of a UK-based programme last year provoked excitement within the scientific community. "Cambridge Uni spins up green and beefy supercomputer project," announced British tech site *The Register*, for example. One reason in particular is because superconducting spintronics might address the eye-watering energy consumption of the huge server farms that handle internet traffic. Data centres account for 3% of the world's electricity supply and about 2% of greenhouse gas emissions.

The project combines two phenomena: superconductivity and spin. Superconductivity refers to the fact that at low temperatures some materials carry a charge with zero resistance. Unlike, for example, copper wires, which lose energy as heat, superconductors are therefore extremely energy efficient.

'Spin' is the expression for electrons' intrinsic source of magnetism. Originally it was thought that this existed because electrons were indeed spinning, which turned out to be wrong, but the name stuck, and it is still used to describe the property in particles that makes them behave a bit like tiny bar magnets. Like a magnet, this property makes the electrons point a certain way; the spin state is therefore referred to as 'up' or 'down'.

Researchers have been using the magnetic moments of electrons to store and read data since the 1980s. At their most basic, spintronic devices use the up/down states instead of the 0 and 1 in conventional computer logic.

Spintronics could also transform the way in which computers process information. The researchers envisage that instead of the devices moving packets of charge around, they will transmit information using the relative spin of a series of electrons, known as a 'pure spin current', and sense these using magnetic elements within a circuit.

By eliminating the movement of charge, any such device would need

less power and be less prone to overheating – removing some of the most significant obstacles to further improving computer efficiency. Spintronics could therefore give us faster, energy-efficient computers, capable of performing more complex operations than at present.

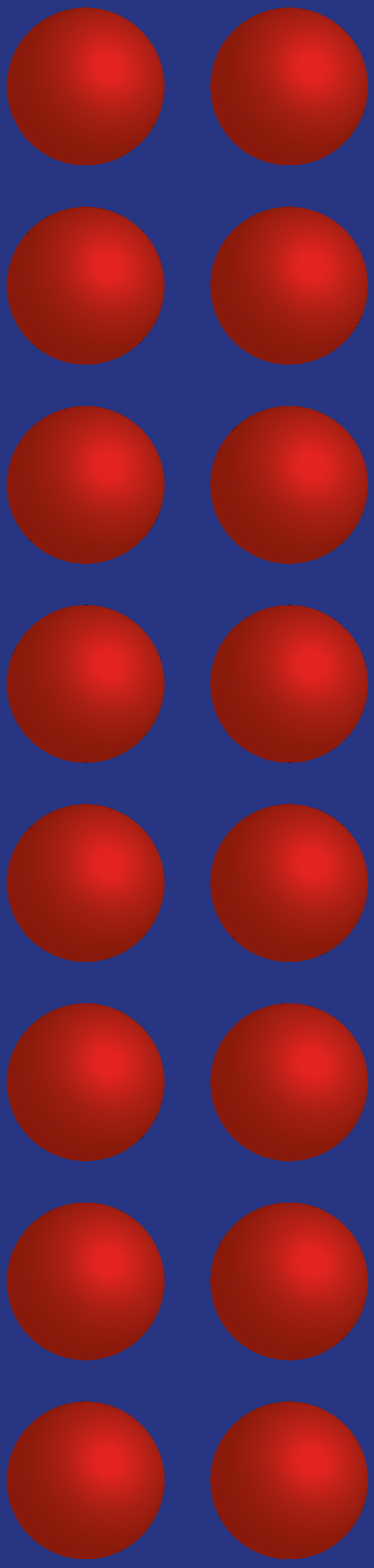
To generate large enough spin currents for memory and logic devices, significant charge is required as an input, and the power requirements of this currently outweigh many of the benefits. Using a superconductor to provide that charge, given its energy efficiency, would present a solution. But the magnetic materials used to control spin within spintronic devices also interfere with superconductivity.

This problem was thought insurmountable until, in 2010, Robinson discovered how to combine superconductors and spintronics so that they can work together in complete synergy. His team added an intervening magnetic layer (a material called holmium). By using this interface, they were able to preserve the delicate balance of electron pairing that's needed to achieve superconductivity, but still managed to create a bias within the overall spin of the electrons.

This, explains Robinson, "created a marriage that opens up the emerging field of superconducting spintronics." Over the next five years, he and Blamire developed the field, and last year were awarded a major grant from the Engineering and Physical Sciences Research Council: "To lead the world in understanding the coupling of magnetism and superconductivity to enable future low energy computing technologies." Robinson has since been awarded a second grant with Professor Yoshi Maeno, from the University of Kyoto, to broaden materials research on superconducting spintronics.

Although still at an experimental stage, the project – which includes collaborators from Imperial College London, University College London and Royal Holloway London – is tackling questions such as how to generate and control the flow of spin in a superconducting system. And its scope is already expanding. "We have found more ways of achieving what we are trying to do than we originally dreamed up," Robinson says.

One example involves making potentially innovative use of superconductivity itself. In 'conventional' spintronics, spin is manipulated through the interactions between magnetic materials within the device. But Blamire has found that when a superconductor is placed between two ferromagnets, its intrinsic energy depends on the orientation of those magnetic layers. "Turning that on its head, if you can manipulate the superconducting state, you can control the orientation of the magnetic layers, and therefore the spin," he says.



Meanwhile, Robinson has led a study that for the first time enabled graphene, a material already recognised for its potential to revolutionise the electronics industry, to superconduct. This raises the possibility of using this extraordinary material, and other two-dimensional materials like it, in superconducting spintronics.

Although approaches like this are still being tested, Blamire says that by 2021 the team will have developed sample logic and memory devices that fuse superconductivity and spin. These proof-of-concept models could, perhaps, be incorporated into a new type of computer processor. "It would be a huge step to get from there to a device that could be competitive," he admits. "It's not necessarily difficult, but it would require considerable investment."

The project is set up to enable industrial collaboration in the years to come. A key partner is the Hitachi Lab in Cambridge, while the project's advisory board also features representatives from the Cambridge-based semiconductor firm ARM, and HYPRES, a digital superconductor company in the USA.

Robinson points out that the UK – and Cambridge in particular – has historical strengths in research into superconductivity and spintronics, but adds that a "grand challenge" has long been needed to focus academic investigation on a meaningful partnership with industry.

Leading low-energy computing into a post-semiconductor age is certainly grand. Silicon's domination, after all, stretches from its eponymous valley in California, to a fen in Cambridge, a gulf in the Philippines and an island in Japan.

Can the unlikely – not to say still primitive – marriage of spintronics and superconductivity really replace an electronic empire on which the sun never sets? "I suspect people had similar questions at the dawn of the semiconductor," Robinson observes. "One shouldn't lose sight of what we are doing here. We aren't just trying to do something better; we are offering something entirely different and new."

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Breath of life

Smoking, lack of exercise, bad diet and our genes are all well-known risk factors for heart disease, cancer and diabetes. But, as researchers are beginning to understand, the environment in the womb as we first begin to grow may also determine our future health.

The history of science is littered with self-experimenters so passionate about their work that they used themselves as human guinea pigs, however ill-advisedly.

Sir Joseph Barcroft (1872–1947) was one such character. Professor of Physiology at Cambridge, he was best known for his studies of the oxygenation of blood. He also led mountain expeditions where he analysed the oxygen content of his blood and that of other expedition members.

In the middle of his career, Barcroft built an airtight glass chamber in his laboratory in Cambridge. There, he could live and exercise at oxygen levels equivalent to 16,000 feet. Like many self-experimentation stories, things did not always go to plan: in one experiment, he had to be rescued by colleagues after spending six days in the chamber and reportedly turning blue.

Despite his occasional misguided venture, Barcroft's scientific legacy was significant and so, in his honour, the University of Cambridge has recently opened a new state-of-the-art facility in his name. Research at the Barcroft Centre focuses on farm animals – mainly sheep and chickens, but also pigs – to model important aspects of human physiology.

The Centre's work spans several areas including Professor Jenny Morton's studies on understanding fatal neurodegenerative diseases such as Huntington's disease and a similar childhood disease, Batten disease, and Dr Frances Henson's work on bone diseases such as osteoarthritis.

However, a significant amount of its work focuses on how we develop in the womb and how this programmes us for increased risk of heart disease in later life. This seems fitting as, in later years, Barcroft became interested in fetal development, and in particular the effects of low levels of oxygen on the unborn baby in the womb.

Carrying on this legacy are Professor Dino Giussani and his postdocs Dr Kim Botting and Dr Youguo Niu. All are also members of the Centre for Trophoblast Research (CTR), which this year celebrates its tenth anniversary and focuses on the interactions between the pregnant mother and the fetus, as mediated by the placenta.

Low levels of oxygen – or hypoxia – can occur in high-altitude pregnancies. But, as Giussani explains, there are far more common causes. "Smoking, pre-eclampsia, even maternal obesity – these all increase the risk of hypoxia for the mother's baby, as do inherited genetic variants," he says.

Housed in the Barcroft Centre is a suite of hypoxia chambers – superficially similar, perhaps, to that in which Barcroft placed himself, but nowadays far more sophisticated (and much safer). These are not intended for humans, but rather for animals, each of which is very closely monitored, often remotely using technology developed by the team.

The smallest of these chambers doubles as an incubator for fertilised hens' eggs. Scientists can watch the development of the fetus directly. They can see how the heart grows, for example, how it is affected by hypoxia, and what effect potential drugs have in ameliorating possible complications.

Of course, we grow in a womb, with a placenta connecting us to our mother and controlling our nutritional intake. Mice and rats are the most commonly used mammals in research, but to model mammalian development in longer-living species with similar rates of development to humans, it is necessary to turn to larger animals. Sheep make a good model. Not only is their gestation – and postnatal life – more comparable to a human's than to a rat's, but a newborn lamb's physiology is also similar in a crucial way to a newborn baby's: its heart is mature at birth. By comparison, a newborn rat's heart is still very immature.

For part of gestation, the sheep are placed in hypoxia chambers, which contain finely controlled, lower-than-normal levels of oxygen. "This reduces the amount of oxygen in the blood of the pregnant sheep and thereby in her fetus," explains Botting. "This mimics conditions where the placenta is not working appropriately, as in pregnancy complicated by pre-eclampsia or maternal obesity."

The pregnant ewes deliver outside the chambers in normal ambient air. Once born, most of the lambs are put out to pasture in the paddocks adjacent to the Centre, where they grow to adulthood.

"The lambs which were hypoxic in the womb are not noticeably different," says Giussani. "The sheep will effectively live a normal life. That is the very point, because underneath, a silent killer is brewing; we want to investigate what happens as they grow because there is a theory that a complicated pregnancy may increase the risk of heart disease in the offspring later in life."

Words
Craig Brierley

Professor Abby Fowden, Head of the School of the Biological Sciences, and another CTR member and user of the Barcroft Centre, says that the facilities are unique. “It’s probably the only centre in the UK that has the capacity – the surgical and care facilities – to do these kinds of long-term developmental and neurodegenerative studies,” she explains.

Like Giussani, Fowden and her collaborator Dr Alison Forhead are interested in how the early environment in the womb programmes us for disease in later life. They are particularly interested in the role of hormones – in both the mother and the fetus – and how they affect growth and development.

There are some conditions, such as hypothyroidism – whereby the body produces insufficient thyroid hormones – and maternal stress, that probably affect normal fetal development, but about which surprisingly little is understood. To model these conditions, Fowden and Forhead again turn to a range of mammals including sheep and pigs.

As Forhead explains, normal development of the fetus is crucial for health in later life. “In the case of many organs, you’re born with a certain number of functional units, and in postnatal life you don’t have the capacity to change that number. So the number you’re born with has long-lasting consequences.”

Take nephrons, for example. These are functional units of our kidneys that filter the blood and are responsible for how much salt and water is excreted into the urine. “If you’re born with fewer nephrons, this has consequences for how much salt you retain, setting you up in later life to be at greater risk of developing high blood pressure.”

What is apparent from this work is just how much of disease in later life is programmed in the womb. While our lifestyle – our diet, how much we exercise after birth – plays an important role in whether we develop heart disease or type 2 diabetes, for example, much of the risk is present before we are even born, programmed during pregnancy into how our DNA and tissues function.

Much of the risk is present before we are even born, programmed during pregnancy into how our DNA and tissues function

“Underneath, a silent killer is brewing”

And these effects don’t necessarily stop at the next generation, as Giussani is discovering in his parallel work with rodents, which allows two or more generations to be studied in a comparably short time.

“If we look at the ‘grandchildren’ of pregnant rats that had a hypoxic pregnancy, we see this disease risk being passed on again, but in a really interesting way,” he says. “A male ‘child’ passes on the cardiovascular risk to the ‘grandchild’, but female offspring confer protection. This is really exciting as inheritable protection against a future risk of heart disease has never been demonstrated in mammals.”

In other words, while we must still recognise our own contribution to our risk of developing certain diseases, some of this risk was programmed into us before we were born: in fact, even before our parents were born. Work at the Barcroft Centre – in monitoring animals for not just one generation but several – will be vital for understanding the consequences of pregnancy not only for our children but also for their children – and even their children’s children.

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Things

India Unboxed

What connects a headhunter's trophy, a meteorite, Hercules, a painting of a Hindu temple, an ornate desk, a brass instrument, a tin of tea (unopened), an exotic orchid, a gharial, stacks of home movies and 8,000 lines of Sanskrit manuscript?

India (and Cambridge).

These items are among the many in Cambridge whose stories are being told as part of India Unboxed, a year-long celebration across the University and city of Cambridge to mark the UK–India Year of Culture 2017.

India Unboxed is rooted in the University's museum collections, and involves academics, local diasporic communities and artists from both India and the UK. The rich programme creatively unpicks the tangled relationships of the two countries, fusing historical context with contemporary perspectives.

And as for the eclectic assortment of items shown here – they collectively represent Cambridge's Botanic Garden, the University Library, the Centre of South Asian Studies Archive and the eight University of Cambridge museums. To find out more about why a tin of Fine Indian and Ceylon Tea was packed for an Antarctic expedition around 1901, how a brass transit instrument was used in the Great Trigonometrical Survey of India and what a gharial actually is, we've made a short series of films to enlighten you.

For more information about the India Unboxed exhibitions, events, digital interventions, discussions and installations, visit www.india.cam.ac.uk

Films available:
http://bit.ly/2qZkNZM

Credit: Cambridge University Botanic Garden, Cambridge University Library, Centre of South Asian Studies Archive, Fitzwilliam Museum, Kettle's Yard (The William G. Congdon Foundation), Museum of Archaeology and Anthropology, Museum of Classical Archaeology, Museum of Zoology, Scott Polar Research Institute, Sedgwick Museum of Earth Sciences, Whipple Museum of the History of Science

FUTURE THERAPEUTICS: THE HUNDRED-YEAR HORIZON SCAN

How will precision medicine define 21st-century therapeutics? What will future healthcare look like? And what actually lies 'beyond the pill'? Chris Lowe, inaugural Director of the Cambridge Academy of Therapeutic Sciences, takes the long view on the future of therapeutics.

It used to be all about fleabane for bites from venomous beasts, mugwort to induce and ease the pain of labour and boiled bedstraw to stimulate clotting. According to Nicholas Culpeper in his 1652 book *The English Physitian*, "a man may preserve his Body in Health; or cure himself, being sick, for three pence charge, with such things only as grow in England".

Prescient words, in some respects – today it's still all about giving the right patient the right drug, at the right dose at the right time, but it's called precision medicine.

In fact, herbal remedies and small-molecule pharmaceuticals have dominated therapeutic medicines since Culpeper's time, before being joined in the 1980s by 'biologics' when it became possible to build new forms of proteins, hormones, receptors and monoclonal antibodies after the DNA code was cracked in Cambridge in 1953.

Science moves fast and we now stand at the threshold of not one but several step changes. New understanding of the structures of cells and systems biology is pioneering the use of human and microbial cells as therapeutic agents. Meanwhile, novel bioelectronic medicines or 'electroceuticals' are shifting the therapeutic approach away from traditional medicines into optics, electronics, instrumentation and software. What will these and other developments in areas such as immunotherapy (see p. 34) and nanotherapy (p. 32) mean to medicine over the next hundred years? And what's taking place now in Cambridge to help this happen?

There seems little doubt that with increased genetic knowledge, precision medicine will define the 21st century.

Future healthcare will have a different geometry... sophisticated diagnostic tools, cloud-based applications and artificial intelligence... an extensive toolbox of therapeutic approaches, all personalised to the individual

The development of massively parallel DNA sequencing by the Department of Chemistry moves us closer to the prospect of sequencing one billion kilobases per day per machine. Genomic information and computational approaches will refine diagnoses, stratify cancer into subtypes, guide personalised treatments and improve the efficiency of clinical trials (p. 36).

Meanwhile, cell-based technologies provide exquisitely selective delivery agents that are naturally able to perform therapeutic tasks. In Cambridge, progress in regenerative medicine promises benefits for replacing human cells, tissues or organs; and the use of stem cells to manage and treat diabetes, degenerative nerve, bone and joint conditions, and heart failure (p. 26).

The convergence of information technologies like augmented reality, cloud-based applications, artificial intelligence and deep learning in digital healthcare will play an increasing role in medical decision support, robotic nursing and surgery, sensors and diagnostics, and so on.

So-called beyond-the-pill services, such as wearables, apps, medical tattoos and point-of-care sensors will offer consumers digital devices for monitoring health and compliance, although issues such as privacy, data integrity and cybersecurity remain concerns to be resolved satisfactorily in the 'internet of people'.

Research into these key future technologies is being conducted in the Departments of Engineering, Materials Science and Physics, and the Centre for the Physics of Medicine. Meanwhile, the newly established Alan Turing Institute and the Leverhulme Centre for the Future of Intelligence bring world-leading expertise in big data, computer science, advanced mathematics and artificial intelligence.

How is the pharmaceutical industry responding to these shifting patterns in modern medical treatments? Global research-based companies have suffered from the downturn in the global economy, the demise of the blockbuster era and the rise in specialist markets. Industry is adapting by placing more emphasis on new therapeutic modalities and repurposing existing drugs, as well as strengthening academic–pharma collaborations at earlier stages of the drug discovery process.

The Milner Therapeutics Institute (p. 23), due to open in 2018, will foster close collaborative interactions between academia and industry to accelerate medical advancement via an 'open borders' paradigm. So too will Apollo Therapeutics, a £40m collaboration between the tech transfer offices of Cambridge, Imperial College London and University College London and three global pharmaceutical industries (AstraZeneca, GSK and Johnson & Johnson) to streamline the academia-to-industry pipeline (p. 20).

New technologies are likely to change the regulatory, legal and policy environments, and business models. For example, some forms of medicine – like gene editing (p. 28) – are both personalised and curative. How will the costs of research, development and marketing for 'cures' be met if the business model is more likely to be a service than a product?

Understanding complex issues such as these will be aided by the networks and convening power established by the Centre for Science and Policy, which coordinates the best scientific thinking to inform public policy, and the Centre for Law, Medicine and Life Sciences (p. 28), which focuses on the legal and ethical challenges at the forefront of biomedicine. Meanwhile, the Institute for Manufacturing is analysing supply chains (p. 30), and the Judge Business School is studying the management of innovation and entrepreneurship.

It's likely that future healthcare will have a different geometry. A complex interplay of patients, industries and service operators will use sophisticated diagnostic tools, digital scrutiny and interpretation using artificial intelligence, and have access to an extensive toolbox of therapeutic approaches, all personalised to the individual patient, and available through a redesigned primary and hospital healthcare environment.

Cambridge is well placed to drive innovation in this highly multidisciplinary therapeutic scenario.

The University has expertise relevant to all stages of the drug discovery, development and manufacturing process, from fundamental biology/chemistry, through drug development and clinical trials, to imaging, safety, delivery, supply-chain management and entrepreneurship.

There's also large-scale investment in research and infrastructure for tackling disease. Take dementia, for instance: more than £17m awarded by the UK Research Partnership Investment Fund will help build a Chemistry of Health building for chemistry-based research in neurodegenerative diseases. Cambridge also hosts one of three UK Drug Discovery Institutes funded by Alzheimer's Research UK (ARUK), and is one of five centres that will form the UK Dementia Research Institute, funded by the Medical Research Council, Alzheimer's Society and ARUK.

Against this backdrop of activity, the Cambridge Academy of Therapeutic Sciences (CATS) has been established to increase the linking of academic research to big pharma, biotech and NHS structures on the Cambridge Biomedical Campus and in the region. The idea is to create a networking, training and enterprise structure that transcends traditional boundaries between clinicians, academics and industrialists, in which fundamental and applied research into diagnostics and therapeutics can flourish and be translated into patient treatments with maximum efficiency.

The time is ripe for this to happen. AstraZeneca's move to Cambridge, combined with close links with GSK and other big pharma companies, as well as the thriving local biotechnology industrial environment and sister institutes like the Wellcome Trust Sanger Institute, provide substantial impetus to co-develop and co-deliver these programmes.

In fact, one might thank Nicholas Culpeper for his vision for the future of medicine and at the same time upgrade his estimate of 'three pence charge' with 36 decades of financial inflation.

www.ats.cam.ac.uk

Words
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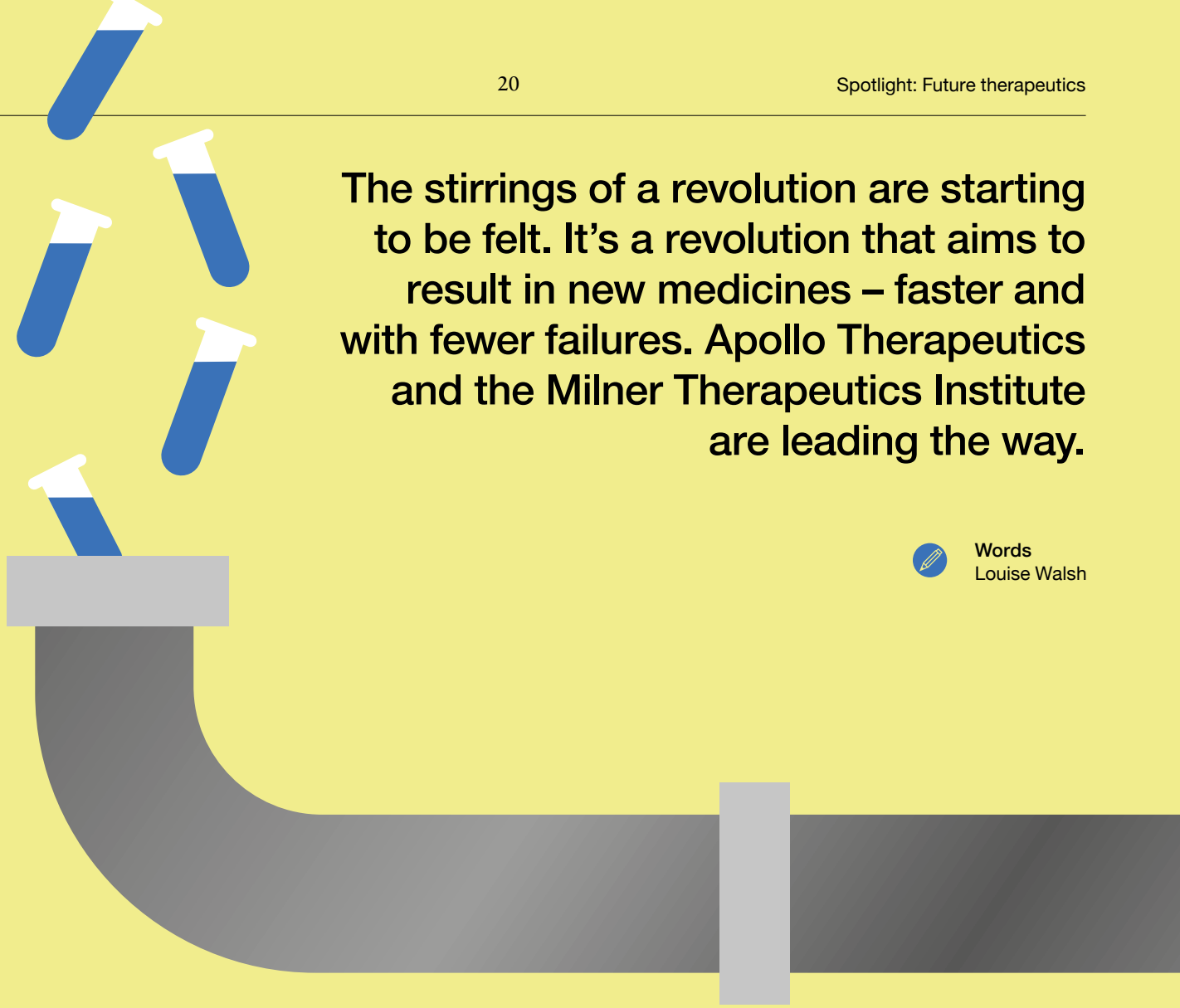


The stirrings of a revolution are starting to be felt. It's a revolution that aims to result in new medicines – faster and with fewer failures. Apollo Therapeutics and the Milner Therapeutics Institute are leading the way.

Words
Louise Walsh

Mission Apollo: find, fund, run

Over the past year, a four-strong team has had over a hundred meetings with scientists at three UK universities. By the end of this year, they will probably have had another hundred.

The team is garnering the most comprehensive sense of what's happening at the bench across three UK universities – Cambridge, Imperial College London and University College London (UCL) – that anyone has ever amassed. Their job is to identify research that has the greatest potential of making it all the way through to becoming a new medicine, and then to help this happen. This is Apollo Therapeutics.

Dr Richard Butt, who heads up the team, explains the drive behind their meetings: "We live in an age of rapidly escalating biomedical innovation – an age where the development of new medicines should be at an all-time high. But the number of new drugs being developed is largely static."

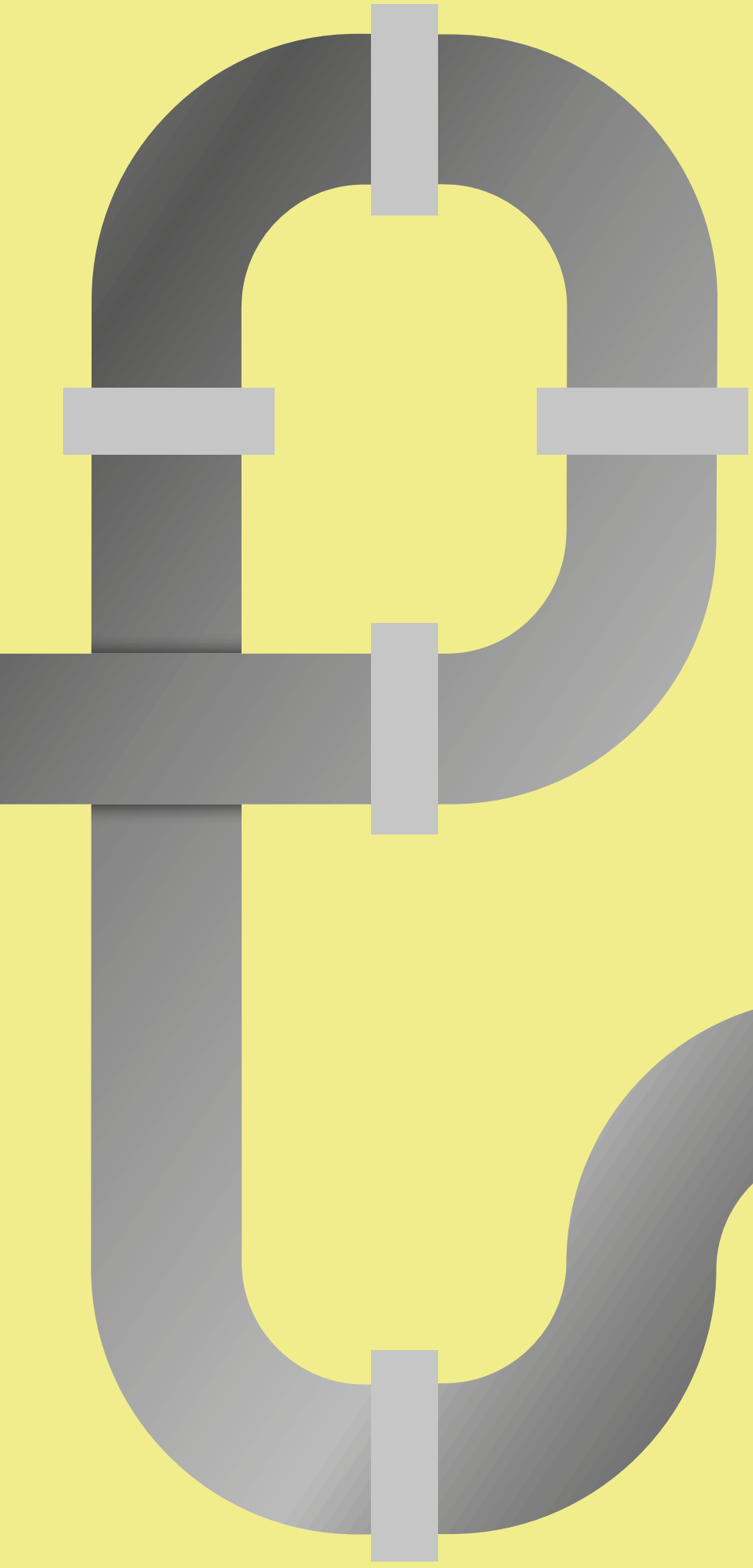
In drug discovery, the period between getting promising results in an academic lab and receiving real interest from an investor or pharmaceutical company has been called the 'Valley of Death' – and not without good reason. Discovering and developing potential new medicines requires not just money but also expertise and the rapid delivery of industrial-type science. Most drug candidates succumb along the way, long before it's possible to know whether they might have fulfilled an unmet medical need.

In January 2016, the tech transfer offices (TTOs) of Cambridge, Imperial College and UCL joined forces with three global pharmaceutical companies – AstraZeneca (AZ), GSK and Johnson & Johnson – to create a £40m collaboration called Apollo Therapeutics. Their aim is to streamline the academia-to-industry pipeline by "finding the best translatable science, funding it fast and running the right development programme to make it attractive to industry," says Butt.

In effect, Apollo aims to maximise the chance that a potential drug will be developed from emerging basic science by investing in a state-of-the-art drug discovery programme that a pharma company will find attractive to license.

"The Apollo approach is wholly new and revolutionary," says Dr Iain Thomas, Head of Life Sciences of Cambridge Enterprise (Cambridge's TTO). "You could say that Apollo is building reassurance. The hardest part of our job at Cambridge Enterprise is selling really good technology to pharma. It relates to the psychology of buying – people don't buy complicated stuff with lots of risk without a lot of analysis. Reassurance comes from being engaged with an opportunity for a long time."

Engagement and partnership are at the heart of the Apollo model. First, Butt's team speaks to the academics and TTOs of the universities to identify exciting prospects, before taking some of the ideas to the wider team of investors (each of the three companies and the TTOs). "As scientists, we will always be very happy to spend time engaging in discussions with any academic about their work. As drug discoverers, we've been very picky about what to take forward,"



he says. “We filter very aggressively to maximise the chance of success.”

Once a project is selected for investment, Apollo and the academics work together to develop the discovery to a stage that will be attractive to a company to license and take further.

This work might take place in the academic’s laboratory, or in one of the pharma companies, or in a contract company. It might also take place at the Milner Therapeutics Institute (see p. 23) – research laboratories that will open on the Cambridge Biomedical Campus in 2018 dedicated to fostering close collaborative interactions between academia and industry.

“The key is the bringing together of the skill sets, philosophies and expertise of those who discover with those who know what to do with that discovery,” says Dr Ian Tomlinson, Chair of Apollo. “We are all motivated by the goal of finding new medicines for patients.”

Tomlinson adds: “The conventional pipeline works like this: an academic does some great science, takes it as far as they are able to within the confines of the lab and then, if they want to take it further, either forms a spin-out or licenses to pharma. This still has its place, but it takes time and is costly. If Richard’s team brings the investment team an idea that looks good, Apollo can fund it and be working with the academic in a matter of weeks.”

Between them, Butt and his three colleagues have over 60 years of experience of the pharma industry. “We’ve been at the sharp end of drug discovery and failure,” he says. “We saw the boom of the late 80s/early 90s of drug approvals. And then genomics,

“We live in an age of rapidly escalating biomedical innovation – an age where the development of new medicines should be at an all-time high”

high-throughput screening and a seeming wealth of targets led to the mindset of 'we can scale this success' – if we run three times more projects we'll be three times more successful'. The basic biology almost ceased to matter. Projects were run that shouldn't have been. R&D costs escalated but the output of new drugs flat-lined or even declined.

"Apollo is led by the science we see. The academic fully understands the biology and mechanisms of the disease target, and we understand the milestones that need to be overcome to become a medicine – drug discovery, formulation, toxicology, clinical trial design, regulators, business models."

Already his team has identified eight projects across the three universities to receive Apollo funding. The first to be backed came out of a 20-year search by Dr Ravi Mahadeva at Cambridge's Department of Medicine for a small molecule drug to treat Alpha-1 trypsin deficiency (AATD). AAT is a protein that normally protects the lungs. In AATD, a single genetic mutation causes it to aggregate in the liver and the resulting effects on the liver and lungs are disabling and ultimately fatal. There is currently no effective long-term treatment for the disease.

"Ravi came to us with an idea and some early compounds," says Butt. "Quite simply, it wouldn't have been picked up by a drug company based on the package that he had. We knew we could design a work package to generate more potent, more selective and more drug-like compounds, and create a package of data that pharma would find attractive."

For Professor Randall Johnson (p. 35), Apollo funds have meant that his research in Cambridge's Department of Physiology, Development and Neuroscience has continued seamlessly through to a drug development programme without the stop-start of waiting for funding, licensing or forming a spin-out. "Randall was one of the first Cambridge academics I saw," says Butt. "He was excited because he was about to publish a key publication on his genuinely novel work highly relevant to the emerging immune-oncology field. Before Randall's *Nature* paper was published, we were already working on a project plan and made the commitment to collaborate on the project.

"Because we are embedded in the University and work closely with Cambridge Enterprise, we have fully confidential access to talk to any academic at any of the three universities. When we worked in pharma, it could take months simply to sit around a table and talk about science and look at data with academics."

Further down the line, potential therapeutics developed from any of the Apollo-funded programmes will first be offered for licensing to AZ, GSK and Johnson & Johnson, and then more widely; the capital gain of any licensing agreements will be divided between the three universities and the three pharma investors. And the interaction with the companies is not just transactional. Each of them is also committing time, resources and expertise to help the projects that are approved for collaboration.

"The cost to license from us will be much lower than the sum cost to have done all that research internally," says Tomlinson. "At a time when all the pharmas are cutting their costs and doing less R&D, this provides a different model that will be cost-effective to add potential drugs to their pipelines.

"There are very few totally new drugs every year. To get one of those, you've got to cast the net very wide and do everything you can to make the most of the opportunities.

"Apollo has the advantage of not being pigeonholed into working only on one disease or therapy area or limited by drug modality, as we would be if we were a pharma company. As a result, we don't have to consider a 'strategic fit' – we're simply following the best translatable science that should result in a higher success in getting new medicines to patients."

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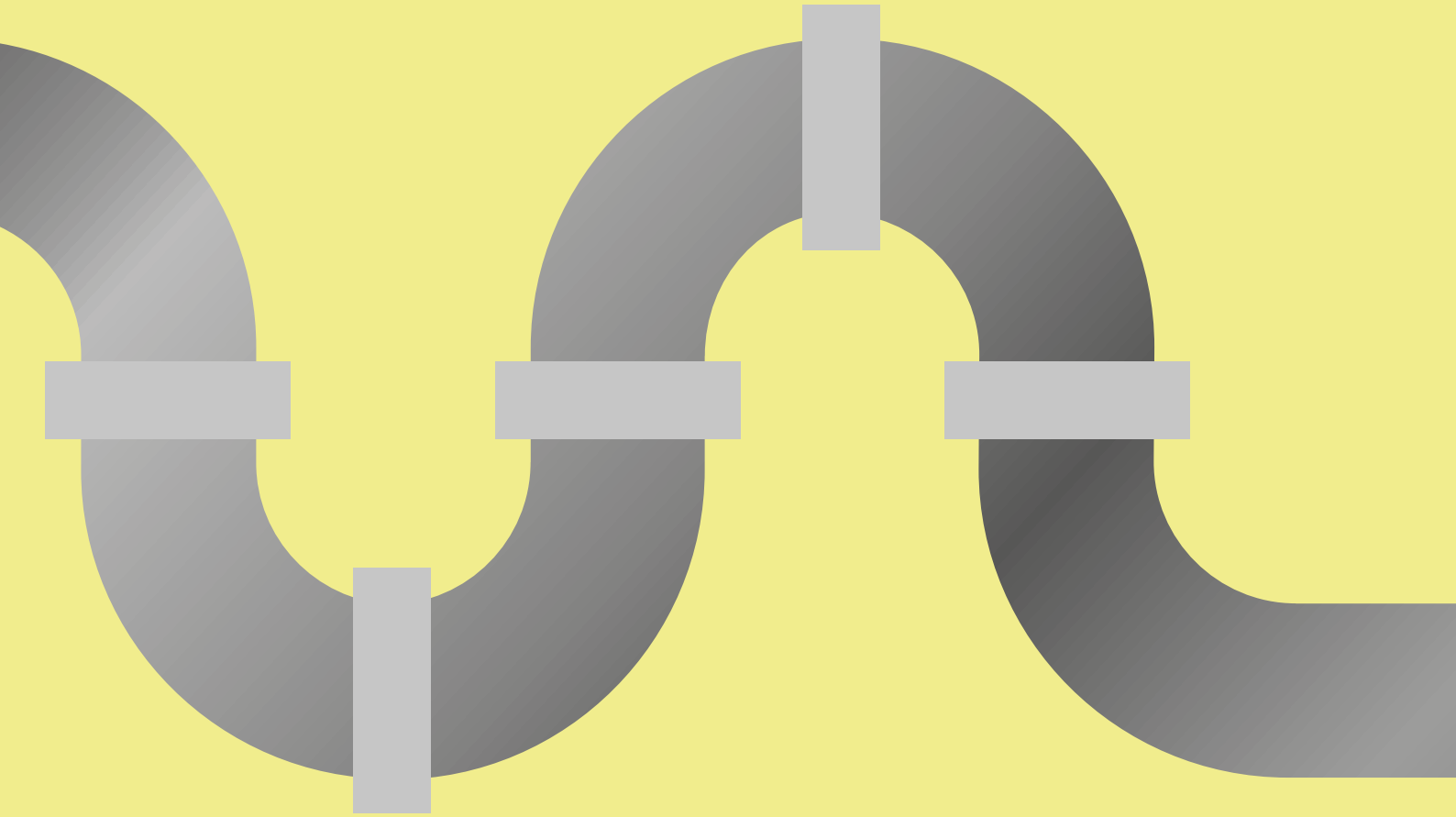

Milner Therapeutics Institute: a drug discovery ecosystem

Tony Kouzarides is passionate about ecosystems: well-balanced communities that flourish on mutual and dynamic interactions. But the ecosystems that excite him are not made up of plants, animals and environments. They're made up of experts.

Professor Tony Kouzarides is the founding Director of the Milner Therapeutics Institute, which is due to open in 2018 on the Cambridge Biomedical Campus. The ecosystem he sees thriving within its walls is one in which academic researchers ("experts in the biology of diseases") work closely with pharmaceutical companies ("who know what's needed to get the drug to clinic") to find new medicines. Put simply, he says, the Institute will be "a pipeline for drug discovery within an academic setting."

While the labs are being fitted out with robotics for customised drug screening, gene-editing facilities to rewrite DNA and bioinformatics support to help scientists deal with huge datasets, the partnerships between industry and academia are already under way.

In June 2015, a research agreement was signed between the University of Cambridge, the Wellcome Trust Sanger Institute and the Babraham Institute with three pharmaceutical companies – AstraZeneca (AZ), Astex and GSK. Since then, Pfizer, Shionogi and Elysium Pharmaceuticals have joined the Milner Therapeutics Consortium, the outreach programme of the Institute.

With this one agreement, doors opened. Dr Kathryn Chapman, Executive Manager of the Milner Therapeutics Institute, explains: "Forming the Consortium means there's now a free exchange of potential drug molecules between pharma and academia. This sounds straightforward but, before the agreement, this could take a year because of confidentiality and material transfer contracts. Now it takes two to three weeks. It lowers barriers of engagement, it speeds up research and it can involve hundreds of molecules in one go."

One consequence is drugs that have already been approved for use in certain diseases are now being tested for use in other diseases – a practice called repositioning or repurposing.

"An academic might have developed a brain disease model using an organoid – a mini organ in a Petri dish," explains Kouzarides. "We can use this to test drugs that have been licensed for use in other diseases such as arthritis or cancer."

It also means that novel therapeutic agents across the entire portfolio of drugs being developed by each of the companies can be screened at an early stage in biological assays, to see whether any are worth progressing along the drug development pipeline.

For example, one of the Consortium's first collaborative projects is a partnership between AZ and Professor Carlos Caldas at the Cancer Research UK Cambridge Institute.

Breast cancer consists of several different genomic subtypes, which makes effective treatment challenging and prognosis variable. Some subtypes respond well to particular drugs or drug combinations whereas others are resistant. Caldas has pioneered the development of a biobank of patient-derived breast cancer cells and tissues that have greater predictive power for clinical outcome than other preclinical models (such as cancer cell lines).Carlos and AZ are now working together to test how different subtypes of breast cancer respond to different AZ compounds and compound combinations, as well as looking at potential drug-resistance mechanisms.

From 2018, the Consortium will form a major part of the Milner Therapeutics Institute, which has been made possible through a £5m donation from Dr Jonathan Milner, a former member of Kouzarides' research group and entrepreneur. Milner and Kouzarides are two of the founders of leading Cambridge biotechnology company Abcam.

"One of the main aims of the Institute will be to develop multiple disease models to understand how drugs could work on the real disease," explains Kouzarides. "We plan to focus on some of the most challenging diseases to start with – cancer, neurodegeneration and inflammation – but we are disease agnostic. If we have a method of testing for efficacy and a library of molecules to test, then we'll test!"

Kouzarides' enthusiasm for making sure the 'Petri-dish-to-pill' pipeline works comes from his own positive experience of a collaboration with GSK that has resulted in a leukaemia drug now being used in the clinic to treat patients.

It came about through serendipity. "GSK was developing a molecule called I-BET against an epigenetic protein. I was a consultant on the project and became aware that the molecule could be effective against mixed lineage leukaemia (MLL), the most common type of leukaemia in children under two years old. We had the cell assays and disease models in Cambridge, and we asked to test the drug. It worked and it's now in the clinic.

"I started to wonder why this pharma–academia collaboration doesn't happen more often. People have been talking about the translational gap between fundamental research and the clinic for years, and it's still there. While serendipity is good – and many amazing medical innovations have come out of chance encounters – we can't trust only to chance.

"The world needs new medicines to be developed. It's time-consuming and costly, and that's why we need an ecosystem that will nurture and speed up the success."

The Milner Institute will be within the Capella building at the Cambridge Biomedical Campus, alongside the relocated Wellcome Trust/MRC Cambridge Stem Cell Institute, the Cambridge Institute of Therapeutic Immunology and Infectious Disease, and The Cambridge Centre for Haematopoiesis and Haematological Malignancies.

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The bug hunters

Words
Becky Allen

Trevor Lawley and Gordon Dougan are bug hunters, albeit not the conventional kind. The bugs they collect are invisible to the naked eye. And even though we're teeming with them, researchers are only beginning to discover how they keep us healthy – and how we could use these bugs as drugs.

Their microbial quarry gives Dr Trevor Lawley and Professor Gordon Dougan an interesting take on the world and human interaction. When we meet at the Wellcome Trust Sanger Institute, where they both lead research groups, we shake hands. For me, it's a social norm; for them, it's a chance to swap bugs.

"When we shook hands, you probably got some of my spores and I got some of yours. It's a form of kinship that we are just starting to understand," says Lawley. "When we think about spreading bugs, we often focus on pathogens and disease. The truth is, pathogens are a tiny proportion of the whole community of diverse microorganisms that are on and within us and there's probably an element of spreading health through this microbiome."

The microorganisms live on our skin, up our noses and – in particularly large numbers – in our gut. The average human intestine harbours some 100 trillion bacteria from 1,000 species. They have around three million genes and make up 3% of our body weight. "We're coated with microorganisms – bacteria, viruses, fungi – they outnumber human cells by at least three to one, so we're more microbial than eukaryotic," he explains.

So what are they all doing there? Although much remains a mystery, we know that changes in the microbiome appear to be linked with health and disease. They produce vitamins we cannot make ourselves and break down food to extract essential nutrients; and they help our immune systems develop and defend us against harmful bugs.

It seems that as well as being a community, our microbiome is also

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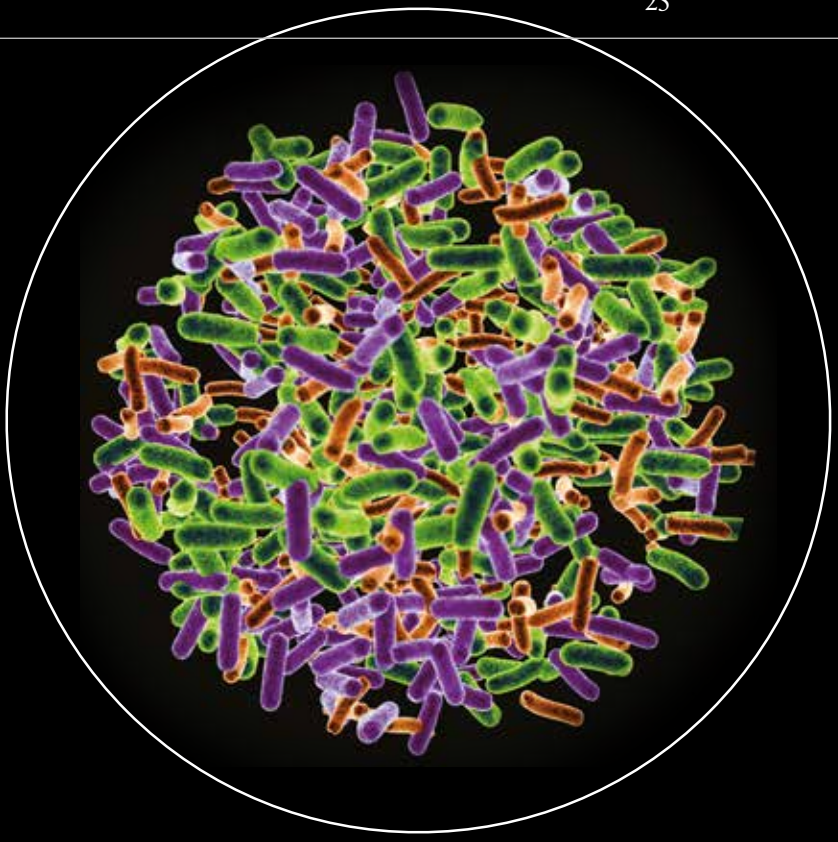


like an organ or tissue. "Some 30–40% of metabolites in our blood come from microbes in the intestine, so lots of our physiology and wellbeing is probably driven by factors in the gut that we don't fully appreciate," says Dougan, who holds a Chair in Cambridge's Department of Medicine. "But we're starting to realise that several human diseases are caused by pathological imbalances in these microbial communities, and that genetics, diet, antibiotics and infections can create these imbalances."

The idea that our microbiome contributes to our health is not new. In 1908, the Russian microbiologist Ilya Mechnikov won a Nobel Prize for his discovery of phagocytes. He also sought to nurture his microbiota by consuming copious quantities of fermented milk, having noticed the longevity of yoghurt-loving Bulgarians.

Since then, the microbiome has been implicated in many areas of health and disease. "Evidence is accumulating that our microbiota can protect us against infection and inflammatory diseases of the bowel, influence factors such as obesity, and that bad microbiota, such as *Clostridium difficile*, can damage us," Dougan explains.

C. diff is a key part of this story. First described in the 1930s, *C. diff* lives in the gut of around 3% of healthy adults and, kept in check by a healthy microbiota, it does no damage. When antibiotics disrupt the microbiota, however, *C. diff* can be life threatening, especially among frail, elderly adults in hospitals and care homes.

In such circumstances what works best is not more antibiotics, but reintroducing gut bugs from healthy volunteers via faecal transplants. While not the most marketable of treatments, its astonishing success led Lawley and Dougan to believe that the microbiome could be an important therapeutic target.

"When I started training in Gordon's lab ten years ago, we realised that faecal transplants could cure 90% of people with *C. diff* who had failed standard antibiotic treatment," says Lawley. "That's when we started to think that if we could identify the good bugs, we could make a medicine."

Unfortunately, identifying the good bugs is harder than it sounds and for many years researchers lacked the necessary tools to culture them, characterise them and chart their modes of action.

Three recent advances changed all that. Genomics has helped us understand the microbiome as a whole. In 2003, scientists at Stanford University sequenced the gut microbiome (the collective genomes of all resident microorganisms) of healthy human volunteers for the first time, and 2008 saw the establishment of the Human Microbiome Project (a United States National Institutes of Health initiative). Then, germ-free mice provided researchers with a model system to test their ideas. Finally, Lawley discovered a way of growing gut bacteria in the lab – something that for decades was thought impossible.

"One of the things we had to overcome – a dogma as well as a technical barrier – was to culture the unculturable," he says. "Now, we are culturing at scale and sequencing. This means we have access to the bugs to follow up and work out what they do, and then even to make a medicine from."

Buoyed by their success, the Sanger Institute last year spun out a new company – Microbiotica – to exploit their unique capabilities in microbiome science, particularly in culture collection, genome database and animal models, to develop new medicines.

"We're collecting samples of poo from around the world – from Vietnam and India to Nigeria and Kenya – to build a globally representative collection of microbiome bacteria. No-one else has such a large and diverse collection," Dougan says. "It will allow us to mine these isolates – and their genomes – for new antibiotics and design new bacterial-based therapies."

As well as finding a more palatable alternative to faecal transplants for *C. diff* infections, Lawley and Dougan have their sights set on using bugs as drugs in other areas. There is strong evidence that both inflammatory bowel disease (which affects around 0.5% of the population) and irritable bowel syndrome (which affects 15–20%) result from a damaged microbiome, so these conditions are prime candidates.

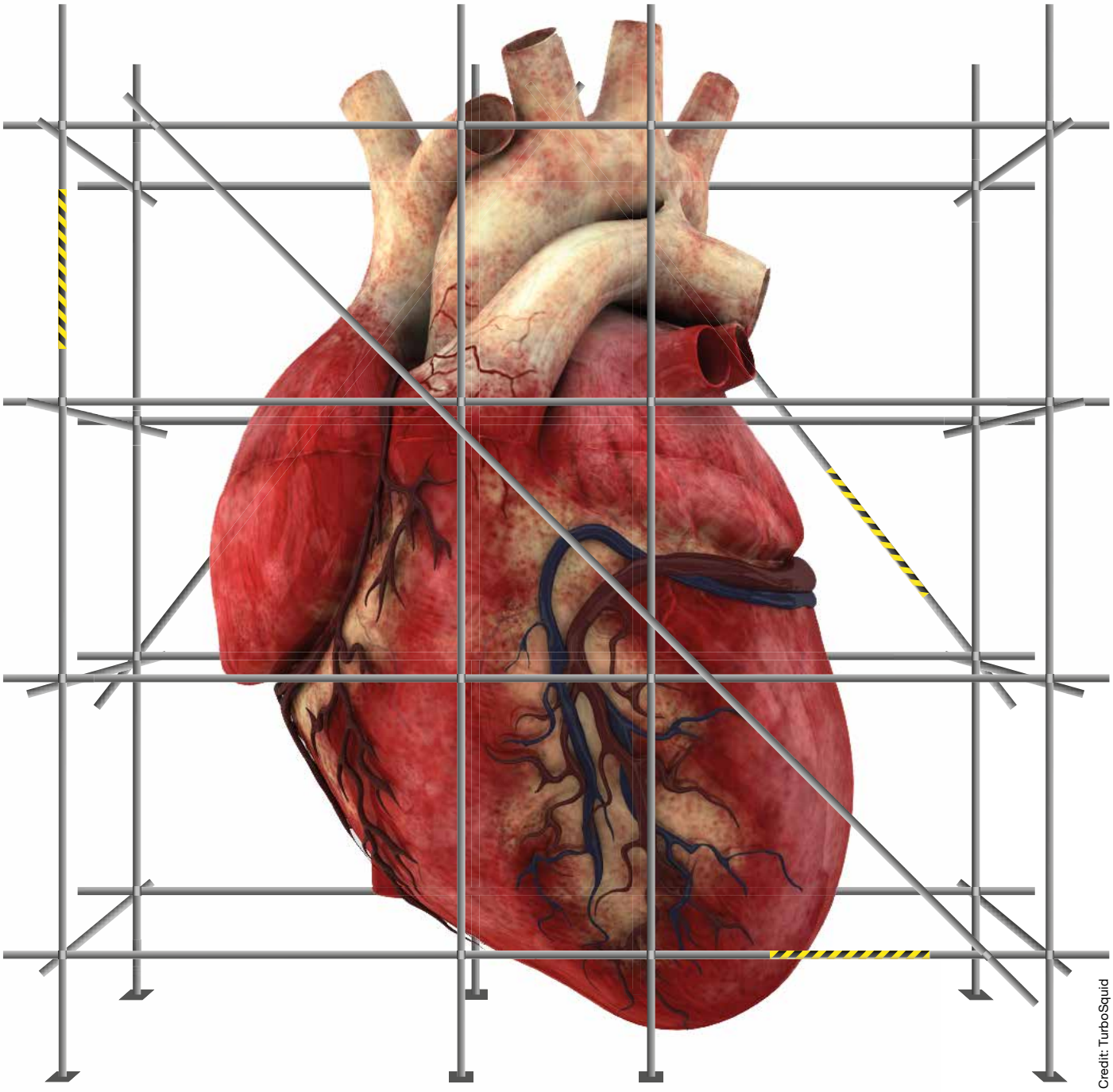
Lawley and Dougan are also working with Imperial College London to study links between the lung microbiome and chronic obstructive pulmonary disease and asthma, as well as the microbiome differences of babies born by C-section versus vaginal delivery. They are also working with American collaborators on the bladder, where the hallmark of a healthy microbiome is very different to that of the gut.

"In the gut, the signature of health is diverse microbes. In the vagina and the bladder, it's the opposite – simplified is healthy. Once they become diverse, there's something wrong," explains Lawley, who is also Chief Scientific Officer at Microbiotica.

The researchers are also working on some cancers for which modern immunotherapies are successful against the disease but cannot be used in some patients because they damage the microbiome so badly. "We're involved in MelResist, a multi-university collaboration on new therapies for melanoma. Long-term survival in melanoma patients treated with antibody therapies is now a remarkable 50%," says Lawley. "But if they have two different antibodies, they can develop life-threatening diarrhoea and colitis and have to stop treatment – we think there's a microbiome element there."

It's a far cry from Bulgarian yoghurt, and while there's much science yet to be done, and many regulatory challenges to bring an entirely new kind of medicine to market, it's a challenge they relish. "We want to innovate and encourage links and partnerships with other organisations," Dougan concludes. "It's a whole new science – but we're confident that we can deliver new medicines."

‘PATCHING UP’ A BROKEN HEART



Credit: TurboSquid

Tiny beating pieces of heart tissue are being grown in Petri dishes. The innovation that makes this possible is a scaffold.

It is almost impossible for an injured heart to fully mend itself. Within minutes of being deprived of oxygen – as happens during a heart attack when arteries to the heart are blocked – the heart's muscle cells start to die.

When the body's repair system kicks in, in an attempt to remove the dead heart cells, a thick layer of scar tissue begins to form. While this damage limitation process is vital to keep the heart pumping and the blood moving, the patient's problems have really only just begun.

Cardiac scar tissue is different to the rest of the heart. It doesn't contract or pump because it doesn't contain any new heart muscle cells. Those that are lost at the time of the heart attack never come back. This loss of function weakens the heart and, depending on the size of the damaged area, affects both the patient's quality of life and lifespan.

"In many patients, not only is their heart left much weaker than normal but they are unable to increase the amount of blood pumped around the body when needed during exercise," explains Dr Sanjay Sinha. "I've just walked up a flight of stairs… it's something I take for granted but many patients who've survived heart attacks struggle to do even basic things, like getting dressed. While there are treatments that improve the symptoms of heart failure, and some even improve survival to a limited extent, none of them tackles the underlying cause – the loss of up to a billion heart cells."

The numbers are stark. "Half a million people have heart failure in the UK. Almost half of them will not be alive in five years because of the damage to their heart. At present, the only way to really improve their heart function is to give them a heart transplant. There are only 200 heart transplants a year in the UK – it's a drop in the ocean when many thousands need them."

Sinha wants to mend these hearts so that they work again. "Not just by a few percent improvement but by a hundred percent."

He leads a team of stem cell biologists in the Cambridge Stem Cell Institute. Over the past five years, with funding from the British Heart Foundation, they have been working with materials scientists Professors Ruth Cameron and Serena Best and biochemist Professor Richard Farndale on an innovative technique for growing heart patches in the laboratory – with the aim of using these to repair weakened cardiac tissue.

"In the past, people have tried injecting cardiomyocytes into damaged hearts in animal models and shown that they can restore some of the muscle that's been lost," says Sinha. "But even in the best possible hands, ninety percent of the cells you inject are lost because of the hostile environment."

Instead, the Cambridge researchers are building tiny beating pieces of heart tissue in Petri dishes. The innovation that makes this possible is a scaffold. "The idea is to make a home for heart cells that really suits them to the ground. So they can survive and thrive and function."

The scaffold is made of collagen – a highly abundant protein in the animal kingdom. Best and Cameron are experts at creating complex collagen-based structures for a variety of cell types – bone marrow, breast cancer, musculoskeletal – both as implants and as model systems to test new therapeutics.

"The technology we've developed for culturing cells is exciting because it is adaptable to a huge range of applications – almost any situation where you're trying to regenerate new tissue," explains Best.

Sinha wants to mend these hearts so that they work again. "Not just by a few percent improvement but by a hundred percent."

Best and Cameron use 'ice-templating' to build the scaffold. They freeze a solution of collagen, water and certain biological molecules. When the water crystals form, they push the other molecules to their boundaries. So, when the crystals are vapourised (by dropping the pressure to low levels), what's left is a complex three-dimensional warren.

"We have immense control over this structure," adds Cameron. "We can vary the pore structure to make cells align in certain orientations and control the ratios of cell types. We are building communities of millions of cells in an environment that resembles the heart."

Cardiomyocytes fare better when they are surrounded by other cell types and have something to hold on to. They use proteins on their surface called integrins to touch, stick to and communicate with their environment. Farndale has perfected a 'toolkit' that pinpoints exactly which parts of collagen the integrins bind best; he then makes matching peptide fragments to 'decorate' the collagen scaffold. This gives cells a foothold in the scaffold and encourages different cell types to move in and populate the structure.

"We don't just want a cardiac scaffold – we want it to have blood vessels and the same mechanical properties as the heart," explains Sinha. "If it's going to contract and function efficiently, it needs a really good blood supply. And the whole three-dimensional structure must be strong enough to survive the hostile environment of a damaged heart."

Meanwhile, Sinha's team pioneered the production of the different cell types needed for the patch. Their starting material is human embryonic stem cells, but they have also taken adult human cells and 'reset' their developmental clock. "In theory this means we can take a patient's own cells and make patches that are identical to their own tissue. That said, millions of people are going to need this sort of therapy and so our focus at the moment is on coming up with a system where a small number of patches might be available 'off the shelf', with patients receiving the nearest match.

The team is completing tests on the ideal combination of scaffold structure, peptide decoration and mix of cells to create a beating vascularised tissue. Next, the researchers will work with Dr Thomas Krieg in the Department of Medicine to graft the tissue into a rat heart. Their aim is to show that the patch makes vascular connections, integrates mechanically and electrically with heart muscle, and contracts in synchrony with the rest of the heart. Once they've accomplished this, they will scale up the size of the patches for future use in people.

"It's exciting," says Sinha. "We are recreating a tissue that has all the components we see in an organ, where the cells start talking together in mysterious and wonderful ways, and they start to work together as they do in the body. Our vision is that this technology will bring hope to the millions of patients worldwide who are suffering from heart failure, and allow them to lead a normal life again."

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SNIP, SNIP, CURE

Most rare diseases are caused by a defect in the genetic blueprint that carries the instruction manual for life. Sometimes the mistake can be as small as a single letter in the three billion letters that make up the genome, yet it can have devastating consequences. What if it could simply be cut out and replaced?

Gene editing using 'molecular scissors' that snip out and replace faulty DNA could provide an almost unimaginable future for some patients: a complete cure. Cambridge researchers are working towards making the technology cheap and safe, as well as examining the ethical and legal issues surrounding one of the most exciting medical advances of recent times.

Dr James Thaventhiran points to a diagram of a 14-year-old boy's family tree. Some of the symbols are shaded black.

"These family members have a very severe form of immunodeficiency. The children get infections and chest problems, the adults have bowel problems, and the father died from cancer during the study. The boy himself had a donor bone marrow transplant when he was a teenager, but he remains very unwell, with limited treatment options."

To understand the cause of the immunodeficiency, Thaventhiran, a clinical immunologist in Cambridge's Department of Medicine, has been working with colleagues at the Great Northern Children's Hospital in Newcastle, where the family is being treated.

Theirs is a rare disease, which means the condition affects fewer than 1 in 2,000 people. Most rare diseases are caused by a defect in the genetic blueprint that carries the instruction manual for life. Sometimes the mistake can be as small as a single letter in the three billion letters that make up the genome, yet it can have devastating consequences.

When Thaventhiran and colleagues carried out whole genome sequencing on the boy's DNA, they discovered a defect that could explain the immunodeficiency. "We believe that just one wrong letter causes a malfunction in an immune cell called a dendritic cell, which is needed to detect infections and cancerous cells."

Now, hope for an eventual cure for family members affected by the faulty gene is taking shape in the form of

'molecular scissors' called CRISPR-Cas9. Discovered in bacteria, the CRISPR-Cas9 system is part of the armoury that bacteria use to protect themselves from the harmful effects of viruses. Today it is being co-opted by scientists worldwide as a way of removing and replacing gene defects.

One part of the CRISPR-Cas9 system acts like a GPS locator that can be programmed to go to an exact place in the genome. The other part – the 'molecular scissors' – cuts both strands of the faulty DNA and replaces it with DNA that doesn't have the defect.

"It's like rewriting DNA with precision," explains Dr Alasdair Russell. "Unlike other forms of gene therapy, in which cells are given a new working gene but without being able to direct where it ends up in the genome, this technology changes just the faulty gene. It's precise and it's 'scarless' in that no evidence of the therapy is left within the repaired genome."

Russell heads up a specialised team in the Cancer Research UK Cambridge Institute to provide a centralised hub for state-of-the-art genome-editing technologies.

"By concentrating skills in one area, it means scientists in different labs don't reinvent the wheel each time and can keep pace with the field," he explains. "At full capacity, we aim to be capable of running up to 30 gene-editing projects in parallel.

"What I find amazing about the technology is that it's tearing down traditional barriers between different disciplines, allowing us to collaborate with clinicians, synthetic biologists, physicists, engineers, computational analysts and industry, on a global scale. The technology gives you the opportunity to innovate, rather than imitate. I tell my wife I sometimes feel like Q in *James Bond* and she laughs."

Russell's team is using the technology both to understand disease and to treat it. Together with Cambridge spin-out DefiniGEN, they are rewriting the DNA of a very special type of cell called an induced pluripotent stem cell (iPSC). These are cells that are taken from the skin of a patient and 'reprogrammed' to act like one of the body's stem cells, which have the capacity to develop into almost any other cell of the body.

In this case, they are turning the boy's skin cells into iPSCs, using CRISPR-Cas9 to correct the defect, and then allowing these corrected cells to develop into the cell type that is affected by the disease – the dendritic cell. "It's a patient-specific model of the cure in a Petri dish," says Russell.

The boy's family members are among a handful of patients worldwide who are reported to have the same condition and among around 3,500 in the UK who have similar types of immunodeficiency caused by other gene defects. With such a rare group of diseases, explains Thaventhiran, it's important to locate other patients to increase the chance of understanding what happens and how to treat it.

He and Professor Ken Smith in the Department of Medicine lead a programme to find, sequence, research and provide diagnostic services to these patients. So far, 2,000 patients (around 60% of the total affected in the UK) have been recruited, making it the largest worldwide cohort of patients with primary immunodeficiency.

"We've now made 12 iPSC lines from different patients with immunodeficiency," adds Thaventhiran, who has started a programme for gene editing all of the lines. "This means that for the first time we'll be able to investigate whether correcting the mutation corrects the defect – it'll open up new avenues of research into the mechanisms underlying these diseases."

But it's the possibility of using the gene-edited cells to cure patients that excites Thaventhiran and Russell. They explain that one option might be to give a patient repeated treatments of their own gene-edited iPSCs. Another would be to take the patient's blood stem cells, edit them and then return them to the patient.

The researchers are quick to point out that although the technologies are converging on this possibility of truly personalised medicine, there are still many issues to consider in the fields of ethics, regulation and law.

Dr Kathy Liddell, who leads the Cambridge Centre for Law, Medicine and Life Sciences, agrees: "It's easy to see the appeal of using gene editing to help patients with serious illnesses. However, new techniques could be used for many purposes, some of which are contentious. For example, the same technique that edits a disease in a child could be applied to an embryo to stop a disease being inherited, or to 'design' babies. This raises concerns about eugenics.

"The challenge is to find systems of governance that facilitate important purposes, while limiting, and preferably preventing, unethical purposes. It's actually very difficult. Rules not only have to be designed, but implemented and enforced. Meanwhile, powerful social drivers push hard against ethical boundaries, and scientific information and ideas travel easily – often too easily – across national borders to unregulated states."

A further challenge is the business case for carrying out these types of treatments, which are potentially curative but are costly and benefit few patients. One reason why rare diseases are also known as orphan diseases is because in the past they have rarely been adopted by drug companies.

Liddell adds: "CRISPR-Cas9 patent wars are just warming up, demonstrating some of the economic issues at stake. Two US institutions are vigorously prosecuting their own patents, and trying to overturn the others. There will also be cross-licensing battles to follow."

"The obvious place to start is by correcting diseases caused by just one gene; however, the technology allows us to scale up to several genes, making it something that could benefit many, many different diseases," adds Russell. "At the moment, the field as a whole is focused on ensuring the technology is safe before it moves into the clinic. But the advantage of it being cheap, precise and scalable should make CRISPR attractive to industry."

In ten years or so, speculates Russell, we might see bedside 'CRISPR on a chip' devices that screen for mutations and 'edit on the fly'. "I'm really excited by the frontierness of it all," says Russell. "We feel that we're right on the precipice of a new personalised medical future."

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TAKE YOUR MEDICINE

Researchers are working with pharmaceutical companies to make improvements across the whole supply chain, from how a pill is made to the moment it is swallowed by the patient.

"Like many people of my age, I have to take pills morning and night. I'm pretty good at taking them in the evenings, mainly because my wife makes me! But, left to my own devices in the mornings, I only remember to take them perhaps one day out of four," says Dr Jag Srai.

"Wouldn't it be fantastic if smartphones could remind patients, capture use and track activity, blood pressure, sugar level, and so on? And if, at the same time, their GP could see this data and call them in if there's a problem?"

He explains that upwards of 30% of prescribed drugs are not taken by patients and, in the case of respiratory drugs, where application is more intricate, 70% are not taken as directed. The numbers vary depending on the type of condition being treated but they are disarmingly high across the board. This has consequences, and not only for the patient. The cost to the taxpayer of drugs that are not being used is considerable and reduces the pot of money available for patient care.

"In a world of scarce resources this in itself seems incredibly wasteful. But there are other reasons to be concerned," adds Srai, who is Head of the Institute for Manufacturing (IfM)'s Centre for International Manufacturing. "Around 50% of patients taking antibiotics don't complete the course. The consequences of this are potentially catastrophic as infections become increasingly resistant to drug treatment. And drugs contain active ingredients which, when disposed of inappropriately, end up as contaminants in our water supply."

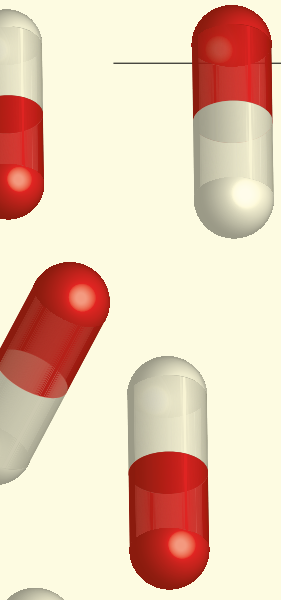
Tackling the thorny problem of patient compliance is just one aspect of the pharmaceutical industry that Srai and his team at the IfM are looking to revolutionise. They are working with other universities and major UK pharmaceutical companies AstraZeneca and GSK to make improvements across the whole supply chain, from how a pill is made to the moment it's swallowed by the patient.

Advances in genetics and biochemistry are helping us move towards a much more tailored approach to medicine, focused on more targeted or niche patient populations, and ultimately the development of bespoke treatments to meet individual patient needs. The implications for how the pharmaceutical industry manufactures its medicines and gets them to the patient are clearly immense.

Most pharmaceutical manufacturing still takes place in huge factory complexes, where large volumes of chemicals are processed in a series of 'batch-processing' steps, and often a dozen or more are required to produce the final oral dose tablet. Developing new drugs is an expensive business and so big pharma companies hope for a 'blockbuster' drug – a medicine that could be used to treat a very common condition, such as asthma or high blood pressure, and which can be manufactured in large quantities.

But, says Srai, the manufacture of these blockbuster drugs is becoming a thing of the past. The batch process is costly, inefficient and makes less sense when producing medicines in small volumes.

New 'continuous' manufacturing processes mean that drugs can be made in a more flow-through model, requiring fewer steps in the manufacturing process, and in volumes better aligned



How new research into pharmaceutical supply chains will help you take care of yourself

Words
Sarah Fell

with market demand. In the case of small volume manufacture, this technology breakthrough can support the move towards more personalised medicine.

"Combine this with the way in which digital technologies are transforming supply chains – through flexible production and automation, using sensors to track location, quality and authenticity, and big data analytics on consumption patterns – and it's clear that the pharmaceutical industry is on the cusp of a huge change," adds Srai.

Recognising this, and to make sure they harness the value these advances in science and technology can deliver, pharmaceutical companies are working together in a number of 'pre-competitive forums'.

The IfM team is playing a key part in two major related UK initiatives: the Continuous Manufacturing and Crystallisation (CMAC) Future Manufacturing Research Hub based at Strathclyde University, funded by £10m from the Engineering and Physical Sciences Research Council and a further £31m from industry; and REMEDIES, a £23m UK pharmaceutical supply-chain sector project, jointly funded by government and industry.

CMAC is focused on the move to continuous manufacturing and REMEDIES on developing new clinical and commercial supply chains. Srai's team is leading the work on mapping the existing supply chains for different types of treatment, and modelling what the future might look like.

"We can envisage a future in which for some medicines, production is no longer a highly centralised large-scale batch operation but one where manufacturing is more about continuous processing, more distributed in nature, smaller scale and closer to the point of consumption."

Asked how local this can become, Srai adds: "In some instances we are already able to 'print' tablet medicines on demand, and we are now exploring whether this might take place at more local production/distribution sites, or at the local pharmacy or even in our own homes. Of course, some critical hurdles still need to be overcome, not least in terms of assuring product quality at multiple sites and establishing appropriate regulatory regimes.

"New technologies are also opening up other possibilities in the way that patients receive healthcare. Wearable and smartphone apps could be feeding diagnostic and health information to our doctors – be they human or (with the advances in artificial intelligence) robot – who would assess our symptoms remotely. We may change our consultation habits completely and only go to the doctor for very specific types of treatment. Indeed, in the UK today, trials suggest some 30% of GP visits are unnecessary."

> "We are already able to 'print' tablet medicines on demand, and we are now exploring whether this might take place at more local sites, or at the local pharmacy or even in our own homes"

As part of the REMEDIES project, the IfM team has been exploring the possibilities presented by technologies that are available now such as Quick Response (QR) codes that can be scanned by mobile apps on our smart phones – and how they can help ensure that patients are taking their medicine.

"A relatively easy thing to do with packaging is to use it as an information source for patients. For example, packs of pills come with a small leaflet that hardly anybody reads. If we want to help patients adhere to their treatment regimes, can we support them by giving them this plus more useful information in a more accessible electronic format?"

The REMEDIES team is working on a mobile phone app that will allow patients to read the instructions on their phone (in a font size and language of their choice) or listen to some explanatory audio or watch a video. "This is simple, readily available technology that could have a significant impact on compliance," says Srai.

The potential for exploiting data to deliver bespoke healthcare in the future is enormous. With smart packaging, smartphones and wearable devices, information can become increasingly dynamic and interactive. Indicators such as time, location – even mood – can affect whether and how drugs are taken; and data such as blood pressure and pulse can show the effect they have on the patient.

"As in the world of e-commerce, we are at the early stages of understanding how this consumer and patient data can inform the supply chain," says Srai. "But we can now contemplate scenarios in certain therapeutic areas, in which each dose a patient takes is fully optimised for the here and now, and manufactured continuously, or even printed on demand."

And if the patient forgets to take it, they will, if they choose, be reminded to do so by a very insistent app.

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How to train your drugs

Drug molecules wrapped in smart, nanoscale-sized packaging could make drugs safer and more effective by delivering treatment only to where it's needed.

Chemotherapy benefits a great many patients but the side effects can be brutal.

When a patient is injected with an anti-cancer drug, the idea is that the molecules will seek out and destroy rogue tumour cells. However, relatively large amounts need to be administered to reach the target in high enough concentrations to be effective. As a result of this high drug concentration, healthy cells may be killed as well as cancer cells, leaving many patients weak, nauseated and vulnerable to infection.

One way that researchers are attempting to improve the safety and efficacy of drugs is to use a relatively new area of research known as nanothrapeutics to target drug delivery just to the cells that need it.

> "Technology that allows us to even imagine these futures"

Professor Sir Mark Welland is Head of the Electrical Engineering Division at Cambridge. In recent years, his research has focused on nanotherapeutics, working in collaboration with clinicians and industry to develop better, safer drugs. He and his colleagues don't design new drugs; instead, they design and build smart packaging for existing drugs.

Nanotherapeutics come in many different configurations, but the easiest way to think about them is as small, benign particles filled with a drug. They can be injected in the same way as a normal drug, and are carried through the bloodstream to the target organ, tissue or cell. At this point, a change in the local environment, such as pH, or the use of light or ultrasound, causes the nanoparticles to release their cargo.

Nano-sized tools are increasingly being looked at for diagnosis (see box), drug delivery and therapy. "There are a huge number of possibilities right now, and probably more to come, which is why there's been so much interest," says Welland. Using clever chemistry and engineering at the nanoscale, drugs can be 'taught' to behave like a Trojan horse, or to hold their fire until just the right moment, or to recognise the target they're looking for.

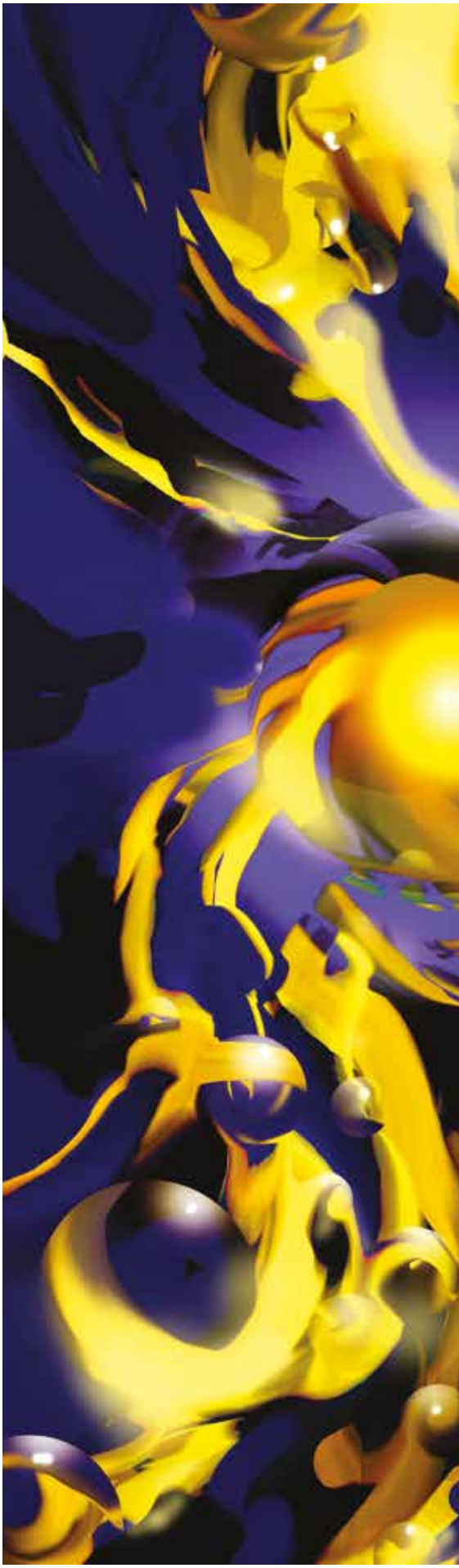
"We always try to use techniques that can be scaled up – we avoid using expensive chemistries or expensive equipment, and we've been reasonably successful in that," he adds. "By keeping costs down and using scalable techniques, we've got a far better chance of making a successful treatment for patients."

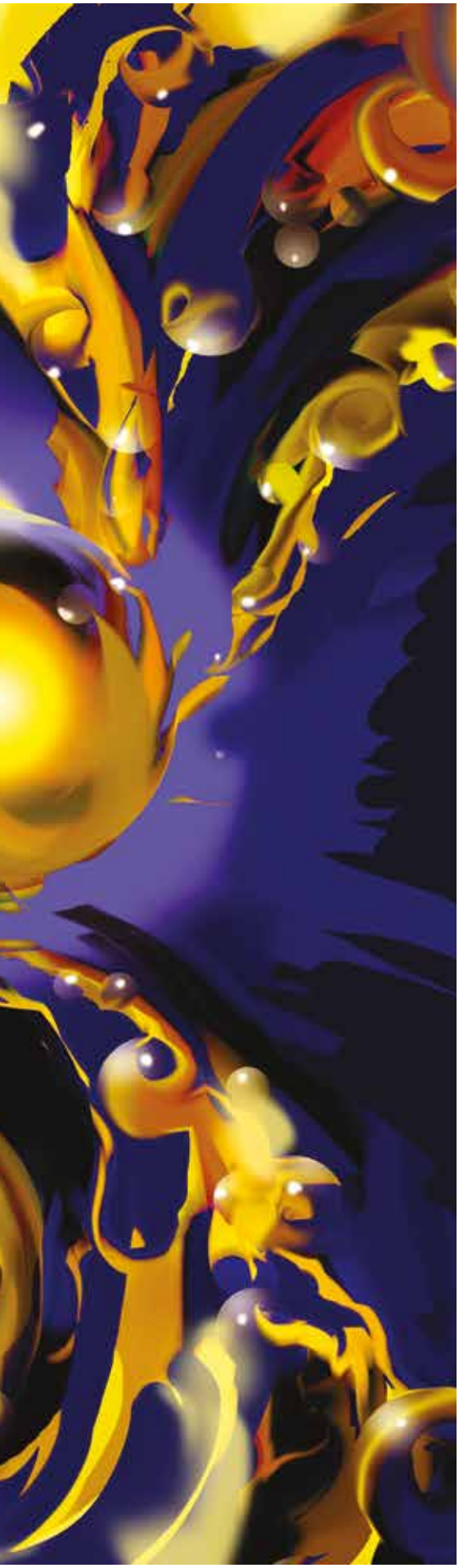
In 2014, he and collaborators demonstrated that gold nanoparticles could be used to 'smuggle' chemotherapy drugs into cancer cells in glioblastoma multiforme, the most common and aggressive type of brain cancer in adults, which is notoriously difficult to treat. The team engineered nanostructures containing gold and cisplatin, a conventional chemotherapy drug. A coating on the particles made them attracted to tumour cells from glioblastoma patients, so that the nanostructures bound and were absorbed into the cancer cells.

Once inside, these nanostructures were exposed to radiotherapy. This caused the gold to release electrons that damaged the cancer cell's DNA and its overall structure, enhancing the impact of the chemotherapy drug. The process was so effective that 20 days later, the cell culture showed no evidence of any revival, suggesting that the tumour cells had been destroyed.

While the technique is still several years away from use in humans, tests have begun in mice. Welland's group is working with MedImmune, the biologics R&D arm of pharmaceutical company AstraZeneca, to study the stability of drugs and to design ways to deliver them more effectively using nanotechnology.

"One of the great advantages of working with MedImmune is they understand precisely what the requirements are for a drug to be approved. We would shut down lines of research where we thought it was never going to get to the point of approval





Credit: Yu Ji

by the regulators," says Welland. "It's important to be pragmatic about it so that only the approaches with the best chance of working in patients are taken forward."

The researchers are also targeting diseases like tuberculosis (TB). With funding from the Rosetrees Trust, Welland and postdoctoral researcher Dr Íris da luz Batalha are working with Professor Andres Floto in the Department of Medicine to improve the efficacy of TB drugs.

Their solution has been to design and develop nontoxic, biodegradable polymers that can be 'fused' with TB drug molecules. As polymer molecules have a long, chain-like shape, drugs can be attached along the length of the polymer backbone, meaning that very large amounts of the drug can be loaded onto each polymer molecule. The polymers are stable in the bloodstream and release the drugs they carry when they reach the target cell. Inside the cell, the pH drops, which causes the polymer to release the drug.

In fact, the polymers worked so well for TB drugs that another of Welland's postdoctoral researchers, Dr Myriam Ouberaï, has formed a start-up company, Spirea, which is raising funding to develop the polymers for use with oncology drugs. Ouberaï is hoping to establish a collaboration with a pharma company in the next two years.

"Designing these particles, loading them with drugs and making them clever so that they release their cargo in a controlled and precise way: it's quite a technical challenge," adds Welland. "The main reason I'm interested in the challenge is I want to see something working in the clinic – I want to see something working in patients."

Words
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Image
Nanotechnology is creating new opportunities for fighting disease – from delivering drugs in smart packaging to nanobots powered by the world's tiniest engines (as depicted in this artist's impression)

Fantastic voyage of the nanobots

Could nanotechnology move beyond therapeutics to a time when nanomachines keep us healthy by patrolling, monitoring and repairing the body?

Nanomachines have long been a dream of scientists and public alike. But working out how to make them move has meant they've remained in the realm of science fiction.

But last year, Professor Jeremy Baumberg and colleagues in Cambridge and the University of Bath developed the world's tiniest engine – just a few billionths of a metre in size. It's biocompatible, cost-effective to manufacture, fast to respond and energy efficient.

The forces exerted by these 'ANTs' (for 'actuating nano-transducers') are nearly a hundred times larger than those for any known device, motor or muscle. To make them, tiny charged particles of gold, bound together with a temperature-responsive polymer gel, are heated with a laser. As the polymer coatings expel water from the gel and collapse, a large amount of elastic energy is stored in a fraction of a second. On cooling, the particles spring apart and release energy.

The researchers hope to use this ability of ANTs to produce very large forces relative to their weight to develop three-dimensional machines that swim, have pumps that take on fluid to sense the environment and are small enough to move around our bloodstream.

Working with Cambridge Enterprise, the University's commercialisation arm, the team hopes to commercialise the technology for microfluidics bio-applications. Their work is funded by the Engineering and Physical Sciences Research Council and the European Research Council.

"There's a revolution happening in personalised healthcare, and for that we need sensors not just on the outside but on the inside," explains Baumberg, who leads an interdisciplinary Strategic Research Network and Doctoral Training Centre focused on nanoscience and nanotechnology.

"Nanoscience is driving this. We are now building technology that allows us to even imagine these futures."

www.nanoforum.cam.ac.uk
www.nanodtc.cam.ac.uk

THE SELF-DEFENCE FORCE AWAKENS

Words
Craig Brierley

Our immune systems are meant to keep us healthy, but sometimes they turn their fire on us, with devastating results. Immunotherapies can help defend against this 'friendly fire' – and even weaponise it in our defence.

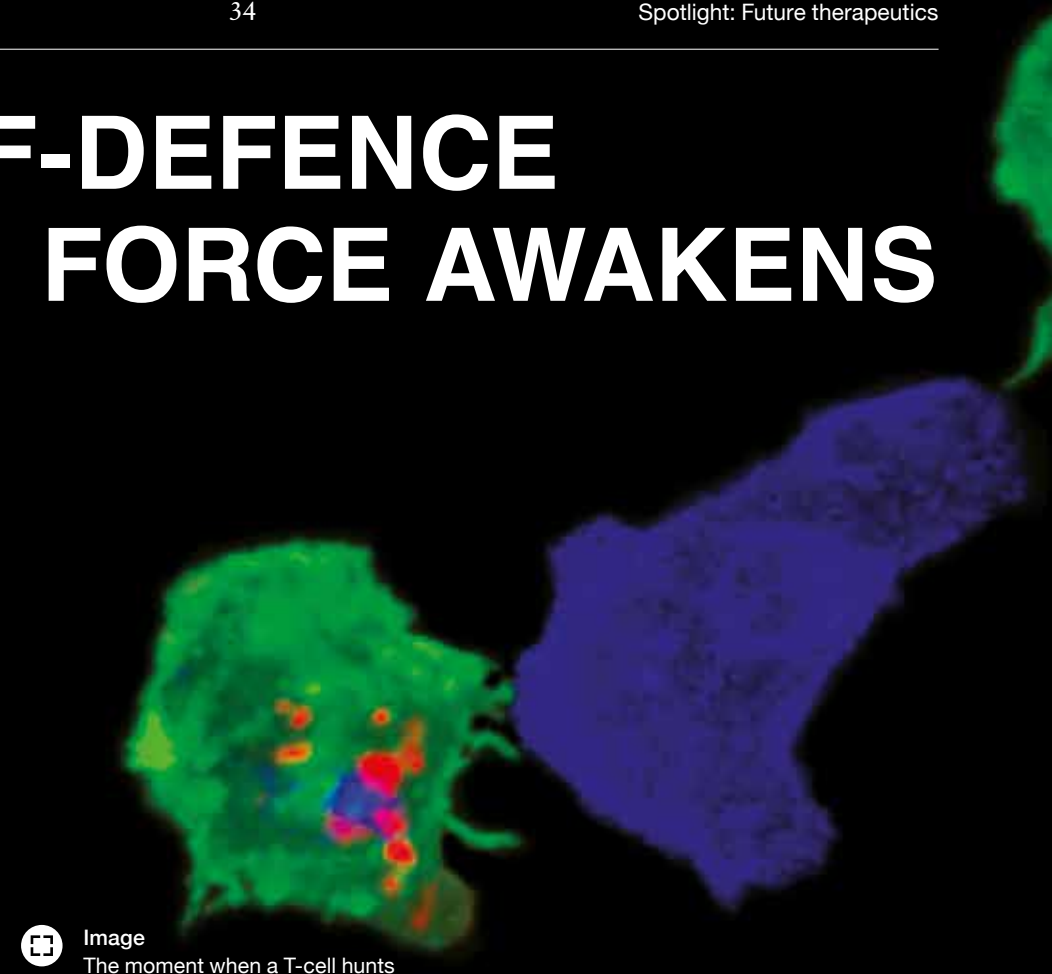


Image
The moment when a T-cell hunts down and eliminates a cancer cell

An army of cells constantly patrols within us, attacking anything it recognises as foreign, keeping us safe from invading pathogens. But sometimes things go wrong: the soldiers mistake benign cells for invaders, turning their friendly fire on us and declaring war.

The consequences are diseases like multiple sclerosis (MS), asthma, inflammatory bowel disease, type 1 diabetes and rheumatoid arthritis – diseases that are increasing at an alarming rate in both the developed and developing worlds.

Cambridge will be ramping up the fight against immune-mediated and inflammatory diseases with the opening next year of the Cambridge Institute of Therapeutic Immunology and Infectious Disease, headed by Professor Ken Smith. The Institute will work at the interface between immunity, infection and the microbiome (the microorganisms that live naturally within us, see p. 24). "We're interested in discovering fundamental mechanisms that can turn the immune system on or off in different contexts, to modify, treat or prevent both inflammatory and infectious diseases," says Smith.

But while diseases such as Crohn's and asthma have long been understood to be a consequence of friendly fire, scientists are starting to see this phenomenon give rise to more surprising conditions, particularly in mental health.

In 2009, Professor Belinda Lennox, then at Cambridge and now at Oxford, led a study that showed that 7% of patients with psychoses tested positive for antibodies that attacked a particular receptor in the brain, the NMDA receptor. This blocked a key neurotransmitter, affecting communication between nerve cells and causing the symptoms.

Professor Alasdair Coles from Cambridge's Department of Clinical Neurosciences is working with Lennox on a trial to identify patients with this particular antibody and reverse its effects. One of their treatments involves harnessing the immune system – weaponising it, one might say – to attack rogue warriors using rituximab, a monoclonal antibody therapy that kills off B-cells, the cells that generate antibodies.

"You can make monoclonal antibodies for experimental purposes against anything you like within a few days," explains Coles. "In contrast, to come up with a small molecule – the alternative sort of drug – takes a long, long time."

The first monoclonal antibody to be made into a drug, created here in Cambridge, is called alemtuzumab. It targets both B- and T-cells and has been used in a variety of autoimmune diseases and cancers. Its biggest use is in MS, where it eliminates the rogue T- and B-cells that attack the protective insulation (myelin sheath) around nerve fibres. Licensed in Europe in 2013 and approved by NICE in 2014, it has now been used in tens of thousands of MS patients.

As well as treating diseases caused by the immune system, antibody therapies are now widely used to treat cancer. And, as Professor Gillian Griffiths, Director of the Cambridge Institute for Medical Research, explains, antibody-producing cells are not the only immune cells that can be weaponised.

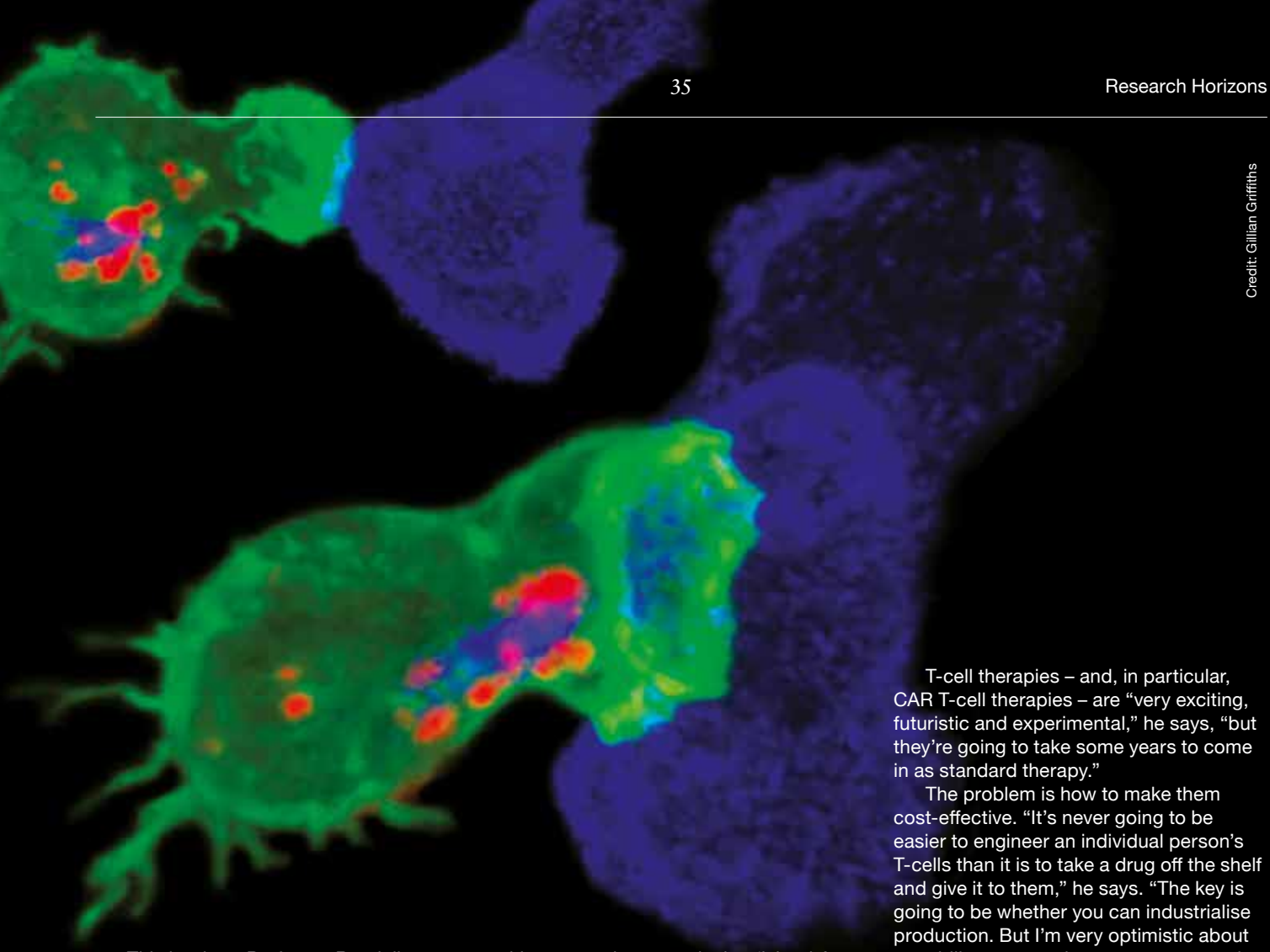
"T-cells are also showing great promise," she says. "They are the body's serial killers, patrolling, identifying and destroying infected and cancer cells with remarkable precision and efficiency."

But cancer cells are able to trick T-cells by sending out a 'don't kill' signal. Antibodies that block these signals, which have become known as 'checkpoint inhibitors', are proving remarkably successful in cancer therapies. "My lab focuses on what tells a T-cell to kill, and how you make it a really good killer, using imaging and genetic approaches to understand how these cells can be fine-tuned," Griffiths explains. "This has revealed some novel mechanisms that play key roles in regulating killing."

A second, more experimental, approach uses souped-up cells known as chimeric antigen receptor (CAR) T-cells programmed to recognise and attack a patient's tumour.

Neither approach is perfect: antibody therapies can dampen down the entire immune system, causing secondary problems, while CAR T-cell therapies are prohibitively expensive as each CAR T-cell needs to be programmed to suit an individual. But, says Griffiths, "the results to date from both approaches are really rather remarkable".

One of the problems that's dogged immunotherapy trials is that T-cells only have a short lifespan. Most of the T-cells transplanted during immunotherapy are gone within three days, nowhere near long enough to defeat the tumour.



Credit: Gillian Griffiths

This is where Professor Randall Johnson comes in. He's been working with a molecule (2-hydroxyglutarate), which he says has "become trendy of late". It's an 'oncometabolite', believed to be responsible for making cells cancerous, which is why pharmaceutical companies are trying to inhibit its action. Johnson has taken the opposite approach.

He's shown that a slightly different form of the molecule plays a critical role in T-cell function: it can turn them into renewable cells that hang around for a long time and can reactivate to combat cancer. Increasing the levels of this molecule in T-cells makes them stay around longer and be much better at destroying tumours. "Rather than creating killer T-cells that are active from the start, but burn out very quickly, we're creating an army of cells that can stay quiet for a long time, but will go into action when necessary."

This counterintuitive approach caught the attention of Apollo Therapeutics (p. 20), who recognised the enormous promise and has invested in Johnson's work, which he carried out in mice, to see if it can be applied to humans.

But T-cells face other problems, particularly in pancreatic cancer, explains Professor Duncan Jodrell from the Cancer Research UK Cambridge Institute, which is why immunotherapy against these tumours has so far failed. The problem with pancreatic cancer is that 'islands' of tumour cells sit in a 'sea' of other material, known as stroma. As Jodrell and colleagues have shown, it's possible for T-cells to get into the stroma, but they go no further. "You can rev up your T-cells, but they just can't get at the tumour cells." They are running a study that tries to overcome this immune privilege and allow the T-cells to get to the tumour cells and attack them.

Tim Eisen, Professor of Medical Oncology at Cambridge and Head of the Oncology Translational Medicine Unit at AstraZeneca, believes we can expect great advances in cancer treatment from optimising and, in some cases, combining existing checkpoint inhibitor approaches.

Eisen is working with the Medical Research Council to trial checkpoint inhibitor antibody therapies as a complement – 'adjuvant' – to surgery for kidney cancer. Once the kidney is removed, the drug is used to destroy stray tumour cells that have remained behind. But even antibody therapies, which are now widely used within the NHS, are not universally effective and can cause serious complications. "One of the most important things for us to focus on now is which immunotherapeutic drug or particular combination of drugs might be effective in destroying tumour cells and be well tolerated by the patient."

T-cell therapies – and, in particular, CAR T-cell therapies – are "very exciting, futuristic and experimental," he says, "but they're going to take some years to come in as standard therapy."

The problem is how to make them cost-effective. "It's never going to be easier to engineer an individual person's T-cells than it is to take a drug off the shelf and give it to them," he says. "The key is going to be whether you can industrialise production. But I'm very optimistic about our ability to re-engineer processes and make it available for people in general."

We may soon see an era, then, when our immune systems become an unstoppable force for good.

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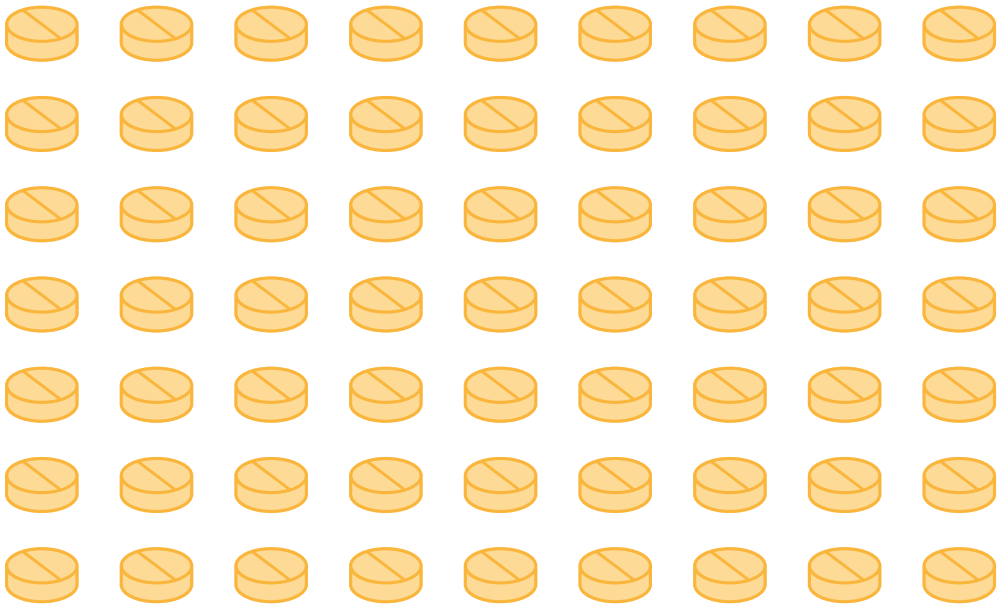
DRUGS: HOW TO PICK A WINNER



Words
Louise Walsh

ENTERING TRIALS

When a drug fails late on in clinical trials it's a major setback for launching new medicines. It can cost millions, even billions, of research and development funds. Now, an 'adaptive' approach to clinical trials and a genetic tool for predicting success are increasing the odds of picking a winner.

"Did not meet primary endpoint."

Prosaic words, but they can mean a billion dollar failure has just happened.

The average cost of taking a scientific discovery all the way through to a drug on a shelf is enormous – last year it was estimated at $2.6 billion by the Tufts Center for the Study of Drug Development.

One reason the figure is so high is because it also includes the cost of failure. Recent years have seen some very high-profile failures of drug candidates that either did not meet the 'primary endpoint' (they didn't work) or had their trials halted owing to serious side effects.

"It's only natural that some drugs will fail in clinical trials – the process exists to ensure that treatments are safe and effective for patients," says Professor Ian Wilkinson, Director of the Cambridge Clinical Trials Unit (CCTU) on the Cambridge Biomedical Campus. "But what's unexpected is the high number of drugs that fail in phase III. You'd think that by this stage the molecule would be a sufficiently good candidate to make it through."

He explains that failures in phases I and II – when the drug is tested for safety and dosage in healthy volunteers and patients – are inevitable. However, a great many molecules don't make it through phase III, the stage at which the drug's effectiveness is tested in large numbers of patients before regulatory approval is given. In fact only 10–20% of drugs that enter phase I are ultimately licensed.

"The problem with failing at phase III is it's very expensive – a single drug trial can cost around $500m."

He continues: "There's a human impact for the thousands of patients who enrolled on the trial. For patients with cancer, it's sometimes their last available treatment option," says Wilkinson. "It's also really unhelpful economically. Pharma companies have less money to put back into R&D, and it becomes even harder to fund drug development."

This is why Wilkinson, along with a team of clinicians, scientists and pharmaceutical collaborators, together with statisticians at the Medical Research Council Biostatistics Unit, has been taking a hard look at the early phases of clinical trials. Their aim is to ask what can be done to get an early indication that a potential drug will make it to market.

"Traditionally, clinical trials have been organised to test safety first and efficacy last," he explains. "It's a cautious step-by-step approach adopted to ensure that pharma companies can satisfy regulators that the drug is safe.

"For many drugs this has worked well. But we are in a landscape where drug targets are more challenging – think for instance of conditions like psychiatric disorders and dementia. Leaving questions of whether a drug is effective to the final stages is now too risky and expensive."

On any one day, the CCTU (one of the UK units accredited by the National Institute for Health Research) might be coordinating up to 20 trials in various phases for potential treatments for cancer, stroke, infections, dementia, heart attack, and so on.

Many of the trials are now designed with what Wilkinson calls "added value" built in at very early stages to give indications of whether the drug might work. This could include a biomarker that shows a drug for cirrhosis is reaching the liver, or a drug for heart disease is lowering cholesterol. "These are read-outs. They don't show the drug works for the disease, but if the results are negative then there's no point in progressing to later stages."

The trials are also run 'adaptively'. "We look at data for each person as it comes in… once we have enough information to guide us, we make a decision that might change the trial. It's a quite different approach to the traditional rigidity of trials. It maximises the value of information a trial can yield."

In recent years, pharmaceutical companies like GSK and AstraZeneca (AZ) have championed the need for rigorous trial design to weed out likely failures earlier in the process.

GSK has its only trials unit in the UK in the same building as the CCTU. There, GSK researchers work alongside Cambridge clinicians and scientists on first-in-man studies. A more targeted approach to testing medicines in patients is a key component of a Strategic Partnership between GSK, the University of Cambridge and Cambridge

“We want to be sure that we can answer the billion dollar question of which are most likely to be winners”

University Hospitals NHS Foundation Trust (CUH), which has the long-term ambition of jointly delivering new medicines to patients in the next five to ten years.

A few years ago, AZ analysed its drug pipeline before embarking on a major revision of its R&D strategy to increase the chance of successful transition to phase III and beyond. One area AZ identified as being crucial to success is to identify a causal relationship between target and disease. This might seem obvious but so-called mistaken causation has led to late failures right across the drugs industry. The usual cause is confounding – where a factor that does not itself cause a disease is associated with factors that do increase disease risk.

Professor John Danesh and colleagues at the Department of Public Health and Primary Care have pioneered a new way of finding evidence for causality before a patient is ever involved. Called ‘Mendelian randomisation’, it’s akin to a trial carried out by nature itself.

“Misinterpreting correlation as causation is a big problem,” explains Dr James Peters, who works with Danesh. “An increase in a protein biomarker in patients with atherosclerosis might suggest it’s important in the disease, but it’s not a valid drug target unless it plays a causal role. The conventional way to test this is to block the protein with a drug in a clinical trial, which is expensive, time-consuming and not always ethical.

“In phase III trials, the randomisation of participants helps to average out all differences apart from whether they are receiving the drug. Instead, we take advantage of the natural randomisation of genetic variants that occurs during reproduction.”

Some genetic variants can increase or decrease certain proteins that have been linked to a disease. If these variants can be identified – by computationally analysing enormous genetic datasets – then researchers can compare groups of people to see whether having the variant also increases the risk of a disease.

The team has used this method to look retrospectively at why two phase III trials for a potential cardiovascular drug failed. “The genetic evidence showed that the drug target was not valid,” says Peters. “We would have advised against taking this drug to a clinical trial.”

But it’s not just about predicting failures, Danesh’s team is picking winners. Evidence for the role of an inflammatory protein in atherosclerosis has now resulted in a clinical trial to see if an arthritis drug can be repurposed for atherosclerosis.

The researchers are helping industrial collaborators to prioritise potential drug targets and predict side effects. They also hope to expand their capabilities to test large numbers of variants for different potential targets in an automated fashion – a high-throughput approach to therapeutic target prioritisation.

Meanwhile, Wilkinson is planning ahead to avoid a different type of limitation: expertise. “There is a lack of individuals trained to design and deliver innovative clinical trials, and this is now impacting on drug development,” he explains.

Last year, an Experimental Medicine Training Initiative was launched to train medics how to run innovative clinical trials. Wilkinson is its Director and it’s supported by the University in partnership with CUH, Cambridge Biomedical Research Centre, and AZ/MedImmune and GSK.

“We all believe that the failure rate for drug candidates making it through phase III is unacceptably high,” he says. “Less than one in a thousand molecules discovered in the lab make it through to being a drug. We want to be sure that we can answer the billion dollar question of which are most likely to be winners.”

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The transplant surgeon who mends bodies and books

The moment I experienced surgery I knew that it was the discipline for me

Credit: © Academy of Medical Sciences, Big T Images http://bigtimages.co.uk/

He revised for his GCSEs with his course books in one hand and a Persian–English dictionary in the other. Today, Iranian-born Kourosh Saeb-Parsy is a transplant surgeon at Cambridge's Addenbrooke's Hospital, where he combines clinical practice with teaching and research. Away from the operating theatre, he is fast becoming an accomplished antiquarian book restorer.

On 30 May, 1989, I walked into a north London comprehensive with my older brother Kasra. I was 13 and he was 14; it was our first day at a new school. With our parents, we'd arrived in the UK a week earlier, flying from Turkey, where we'd spent ten anxious months waiting for a visa. We'd left our home in Iran with two suitcases, and starting school in a new country and different language was tough – the culture shock was immense.

Kasra and I had done a year of English at school in Tehran so we were far from fluent. We joined a group of other children in an intensive English language class. At the end of the school day, the teacher suggested we joined a maths class. Kasra and I sat at the back. I still remember the maths teacher's name: Mrs Barker. We didn't understand a word she said but when she drew a right angle triangle on the board, I knew she was asking the class how to calculate the length of the hypotenuse.

I put up my hand and said the Persian word for Pythagoras – but no-one understood. I walked to the front of the class, took the chalk from Mrs Barker's hand, and wrote the formula on the board. Something of the courage of our parents, who'd sacrificed so much for our future, had seeped into us. We were determined to do well and, though the school ranked low in the borough league tables, we thrived. I'm still in touch with some of our teachers: they're among my closest friends.

In Iran you start school aged six: I'd been furious when Kasra had begun school without me. Each day when he came home, he'd teach me what he'd learnt. When I too started school, I did his homework as well as mine. Eventually I was allowed to skip a year. Arriving in the UK, we were put in the same school year. From early on, both of us wanted to be doctors. Today I'm a transplant surgeon at Addenbrooke's and Kasra is a urology surgeon in the same hospital.

The moment I experienced surgery I knew that it was the discipline for me. The combination of the intellectual challenge and the hands-on craft of surgery – plus the need to work closely with colleagues in other disciplines – suits me perfectly.

I became a University Lecturer and Consultant Transplant Surgeon in 2012. My clinical work involves kidney, pancreas and liver transplantation and laparoscopic (keyhole) surgery to enable a person to donate a kidney to someone else. Much of my work is done as an emergency and out of normal working hours, but I'm fortunate to work as part of a great team. I also run a research group with several PhD students, all of whom do multidisciplinary translational research projects in collaboration with other labs in Cambridge.

About six years ago I began collecting old books. I've always loved books – as works of art as well as vehicles for ideas. At a book fair in Cambridge, I met an antiquarian book restorer called Anthony Thomlinson. He'd studied at St John's College, Cambridge, and worked in advertising before concentrating on what he loved. I asked him to restore some books and began to get really interested in his craft. It took me six months to persuade him to begin to teach me how to restore and bind books.

What appeals to me is the idea of giving something – or someone – a new lease of life. I have a deep need to fix things – which often means carefully picking them apart and reassembling them. With books it's all about understanding how they were made and with what materials and techniques. I've become a kind of apprentice to Anthony, who insisted I learnt all the stages of book binding. I started by making paperback books from scratch before moving on to rebinding and eventually restoring books.

At home I have a collection of around 750 books – they include medical texts as well as works of history, poetry and literature. My oldest book is the works of Aristotle dating from 1563. This volume had lost its covers and was falling apart. I have rebound it in sympathetic 16th-century style and it should hopefully last another 500 years. I've gradually taken over a spare room at home and turned it into a studio. In my lessons, I spend a couple of hours working in Anthony's workshop under his expert eye. Among my current projects is a very large medical atlas from the mid-19th century.

Antiquarian books exist in ever-diminishing numbers. They're precious items and we need to look after them. Also in short supply are the craftspeople who make the materials and tools you need to create or recreate a beautiful book.

One of the pleasures of working as a transplant surgeon is the network of friendships that develops between colleagues across institutions. It's very similar with books. In the end, it's all about people and their enthusiasm for what they're doing.

People make Cambridge University unique. Cooks, gardeners, students, archivists, professors: all have a story to share. Read other stories in our new series This Cambridge Life.

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Interview
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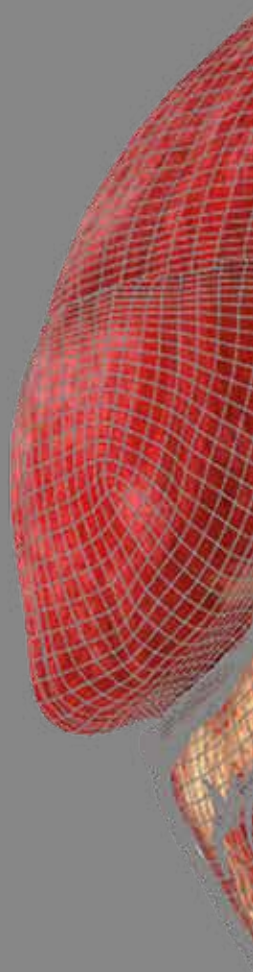

“We are recreating a tissue that has all the components we see in an organ, where the cells start to work together as they do in the body” p. 26

Credit: Jonathan Settle