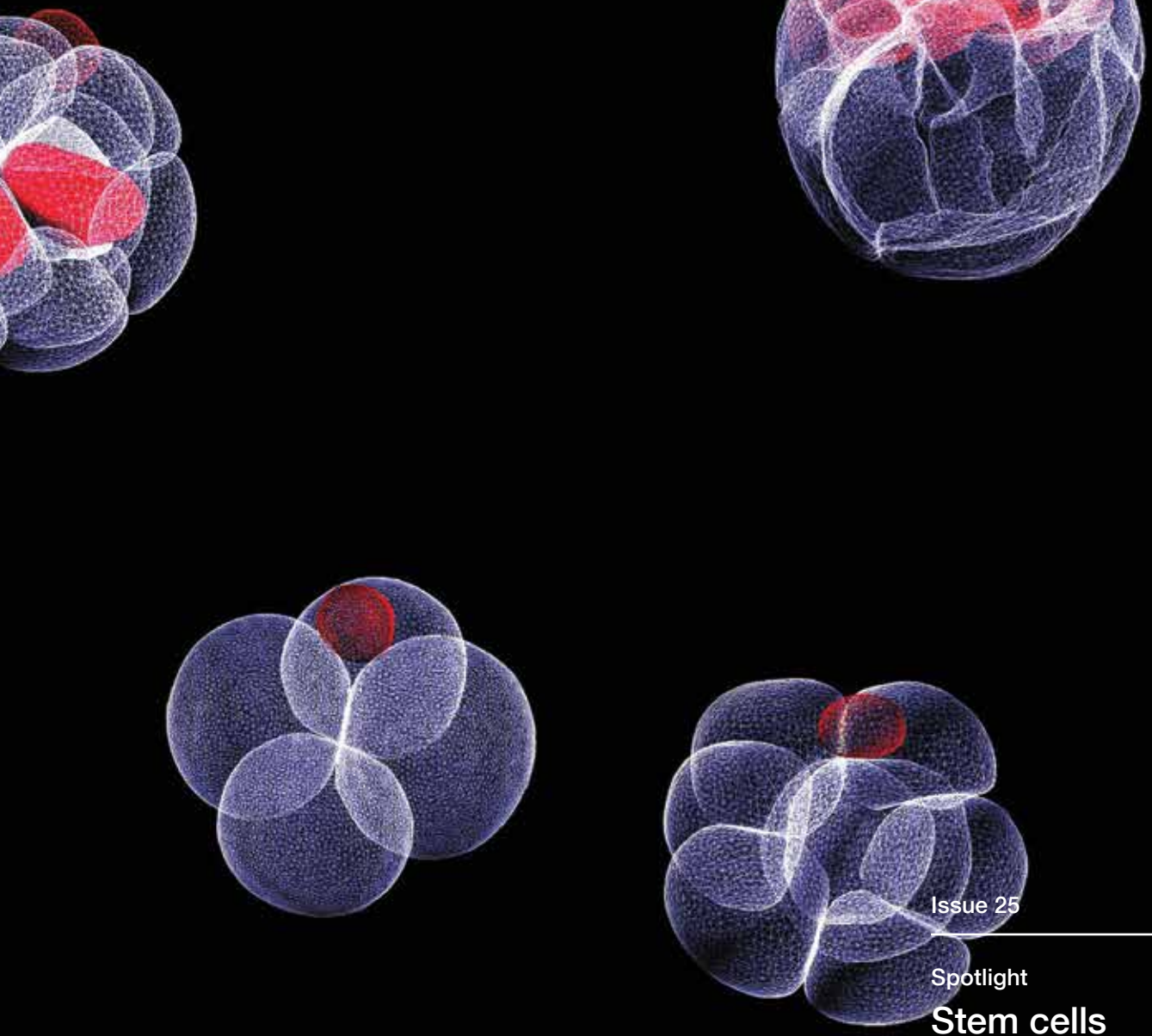
Research

Horizons

Pioneering research from the University of Cambridge



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UNIVERSITY OF CAMBRIDGE
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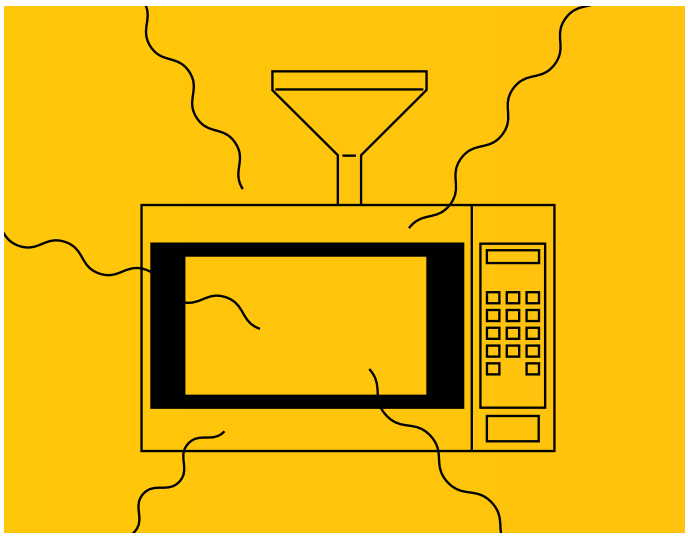

Welcome

Stem cells are one of Cambridge's real success stories. We have won two Nobel Prizes in this area – Sir Martin Evans and Sir John Gurdon were both made laureates for their discoveries. Our Wellcome Trust-MRC Cambridge Stem Cell Institute is a world-leading research centre, and stem cell research has long been a strategic priority for our University.

In this issue, we explore these remarkable cells, which can make every type of tissue in the embryo, repair the body throughout life and renew themselves indefinitely. Now, as researchers delve deeper into their biology, a host of potential uses are coming to light, from supplying new cells to replace damaged tissues, to boosting the body's own repair mechanisms, to providing experimental models for testing new drugs.

Funds are now being raised for a new building for our expanding Institute, scheduled to open in 2018 on the Cambridge Biomedical Campus, where research scientists, technology specialists and medics will work together to make the most of the opportunities afforded by these body 'repair kits'.

Moving from the mini to the massive, Iceland's Bárðarbunga volcano has recently been showing signs of increasing unrest. Cambridge scientists have been monitoring its activity, as well as that of volcanoes worldwide, with the hope of helping to underpin future hazard forecasting.

In a rather less scientific method of forecasting, ancient Mesopotamians believed that the gods inscribed the future on the liver of sheep. In our Extreme Sleepover article, we hear about one researcher's travels to rural Armenia to observe what liver diviners might have seen 4,000 years ago.

All this plus articles on fashion (at a time when it was a finable offence to wear Spanish breeches), the trustworthiness of banks, brain training, visual narratives of plague, and technology that can turn toothpaste tubes into aluminium and fuel in three minutes. We hope that you enjoy this issue.

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News

Monitoring Bárðarbunga

Image
Lava fountains in the recent eruption

Cambridge scientists have been at the forefront of monitoring the activity of the Bárðarbunga volcanic eruption in Iceland.

Bárðarbunga is huge – its volume of magma at the time of writing was already more than twice the size of that which caused the Eyjafjallajökull eruption and ash cloud in 2010, which led to the cancellation of more than 100,000 airline flights.

Since 2006, researchers led by Professor Bob White of the Department of Earth Sciences have been monitoring volcanism in the region, funded by the Natural Environment Research Council.

In the long term, the data will yield considerable new insights into how molten rock moves underground and how this relates to the risk of eruption: "Analysing the data collected since the eruption started probably amounts to around 100-person-years' worth of work," said Professor Simon Redfern, one of the researchers.

But, in the short term, the researchers and PhD students have been key in the 24/7 monitoring of the progress of Bárðarbunga's volcanic activity. Working with the Icelandic Meteorological Office (IMO) and the Earth Sciences Institute of the University of Iceland, the team has been measuring the activity of millions of cubic metres of magma and the rifting of a huge length of dyke as it moves towards the nearby Askja volcano. The aviation and civil hazard warnings in place in Iceland depend heavily on the IMO tracking of this seismicity.

"The massive eruption of Askja in 1875 led to the depopulation of northeast Iceland as ash-fall made subsistence farming impossible," said White. "That is why continued monitoring is so important."

Follow researchers Tobba Ágústsdóttir @fencingtobba and Simon Redfern @Sim0nRedfern on Twitter for the latest developments

Green award for 'unprinting'

University of Cambridge spin-out wins award for technology that removes print from paper.

Laser 'unprinters' that remove toner from paper are a little closer to coming to an office near you.

Every year, one office employee can use up to 10,000 sheets of paper, most of which are thrown away. This new technology has the potential to reduce the number of trees used in the paper life cycle, and could also save an additional 50–80% in carbon emissions over recycling.

Now, Cambridge spin-out company Reduse, which is developing the technology, has been named winner of the Venture Competition, organised by the EU's main climate innovation initiative, Climate-KIC UK.

The 'Unprinter' was invented by Dr David Leal, Reduse's Chief Scientist, during his PhD research with Professor Julian Allwood in the Department of Engineering.

"This award is more proof that we are on the right track to solving the incredible waste that is being generated by printing," said Hidde-Jan Lemstra, CEO of Reduse, which has started raising its first round of funding to complement the Climate-KIC support and a grant from the Technology Strategy Board.

www.reduse.co.uk

News in brief

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

12.09.14

Cambridge University Library has raised £1.1 million to secure one of the most important New Testament manuscripts.

01.09.14

A new study shows that healthier diets and reducing food waste are needed to ensure food security and avoid dangerous climate change.

Why marvellous isn't awesome any more

'Marvellous' has been consigned to the dustbin of vocabulary and replaced by the American 'awesome', according to a new study by Cambridge University Press and Lancaster University.

'Marmalade' has fallen out of favour, 'two weeks' is used more frequently than 'fortnight' and 'essentially' has risen dramatically.

These are some of the early findings of a study using the Spoken British National Corpus 2014, a very large collection of recordings of real-life, informal, spoken interactions between speakers of British English from across the United Kingdom.

Researchers at Cambridge University Press and Lancaster University's Faculty of Arts and Social Sciences have embarked on the first large-scale study in decades to evaluate how the language is used in different regions, between genders, and across age groups and socio-economic status.

The researchers are now calling for people all over the UK to send MP3 files of their everyday, informal conversations to help them delve deeper into spoken language.

"We need to gather hundreds, if not thousands, of conversations to create a spoken corpus so we can continue to analyse the way language has changed over the last 20 years," said Lancaster's Professor Tony McEnery.

Cambridge University Press is greatly experienced at collecting huge amounts of data on how English is used and has the infrastructure in place to undertake such a large compilation project. Linguists at Lancaster University have the expertise to ensure that the resource will be as useful and accessible as possible for further research.

Submit recordings to the research team at corpus@cambridge.org

Ending violence

New evidence presented at the first Global Violence Reduction Conference, in Cambridge, shows that homicide rates in many countries are falling.

Homicide has had a higher body count this century than all wars combined – some 8 million people since 2000. Domestic violence costs the world $8 trillion annually, and around 30% of women have experienced it; one in seven children on the planet is thought to be a victim of sexual abuse.

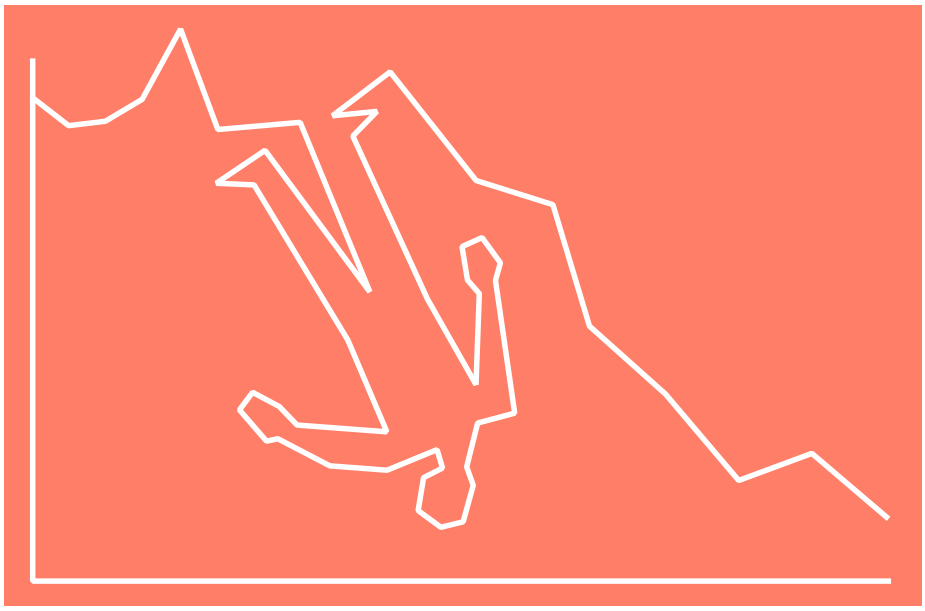
However, amid these sobering facts there is cause for optimism. New evidence presented by Professor Manuel Eisner, director of Cambridge's Violence Research Centre in the Institute of Criminology, shows that homicide rates have been declining since the mid-1990s in many parts of the world – in some cases dramatically.

The new findings are part of a body of research into effective policing strategies, rehabilitation methods, better child protection services and societal attitude shifts – which has many experts agreeing that global rates of violence could be halved by just 2040 if the right policies can be defined and implemented.

Nations as diverse as Estonia, China, South Africa, Poland and Russia have seen average recorded homicide rates drop by 40% or more in the course of just 15 years. Out of 88 countries where trend data could be found, 67 showed a decline and only 21 showed an increase between 1995 and 2010, the new analysis of data from the United Nations Office on Drugs and Crime has revealed.

"Examples of successful homicide reduction can be found across the world. But if we want to achieve a worldwide decline in homicide we need to learn from these success stories and understand what they did right," said Eisner, co-convener of the first Global Violence Reduction Conference.

Eisner and his team will be working closely with researchers from every continent to develop policy recommendations, and to strengthen the knowledge base and research capacity needed to address violence more effectively in low and middle income countries.



11.08.14

New 3D reconstructions show how some of the earliest animals on earth developed and provide some answers as to why they became extinct.

10.07.14

Undernourishment during pregnancy can increase the risk of developing obesity and type 2 diabetes in children, and their children.

18.06.14

More than half of English homes fall short of modern space standards, calling into question the premise behind the so-called bedroom tax.

“Trust me, I’m a banker”

In a post-crash economy, the financial industry has taken a severe hammering in the courts of public approval. Banks have never been trusted less. In a capitalist society, that’s not good news. But now bankers may have some unlikely new saviours: philosophers.

“I’ll pay you, you know, 50,000 dollars, 100,000 dollars… whatever you want… I’m a man of my word.”

A UBS investment banker and ‘man of his word’ is caught trying to bribe a broker. Taken from an incriminating email uncovered after the Libor-fixing scandal – when traders illegally manipulated London interest rates – the sentence illustrates a climate that has a global sector reeling.

Even before news of the scandal broke, PR giant Edelman’s annual Trust Barometer was reporting that public trust in banks had fallen off a cliff, concluding that banking is the “most distrusted global industry.”

People need money. Once they have it, they need to know it’s safe. So people need to trust banks, and banks need people to trust them. If that trust ebbs, the system becomes dangerously unstable. For two philosophers, the current lack of trust sits like a time bomb at the heart of global capitalism.

“One should start by distinguishing trust from trustworthiness. Trust isn’t always valuable, since it may be badly placed. It would be foolish and foolhardy to trust banks when they don’t merit it. Trustworthiness comes first,” said Alex Oliver, Professor of Philosophy at Cambridge. With Professor Boudewijn de Bruin from the University of Groningen, he is co-leading a €1 million, five-year project on Trusting Banks, funded by the Dutch Research Council.

“We are way beyond cheap PR exercises. If the public are to trust banks again, we must promote the key institutional virtues needed for banks to be trustworthy.”

The mid-1980s deregulations were based on the idea that banks have a strong, self-interested reason to behave scrupulously. If they do not, so the reasoning goes, they will be found out, their reputations will suffer and trust will be lost, leading to competitive disadvantage. But this market-based deterrent mechanism has comprehensively failed: witness Bernie Madoff’s Ponzi investment scheme – described as the largest financial fraud in US history – the manipulation of markets, money laundering, mis-selling of payment protection insurance and interest rate swaps, flawed credit ratings and the subprime mortgage crisis. Where will it end?

As those at the top of the sector continue to walk away from financial meltdown with personal fortunes intact, public anger at perceived injustice has mounted. Whether or not banks and their staff deserve this reputation, in the post-crash economic winter there are few, if any, professions and institutions as universally reviled.

For Oliver and De Bruin, this poses a very serious problem. If citizens and businesses distrust banks, they say, a chilling effect will spread as economies slow, unemployment rises and companies and countries go bust. It’s already happening.

“If you talk to bankers, many will blame the public for not trusting them, either for a lack of financial understanding, or for an unwarranted cynicism encouraged by hostile portrayals in the media,” said De Bruin, “but this is a defensive ‘blame the consumer’ strategy – a form of denial. The decline in public trust tracks a decline in trustworthiness of the financial sector. Trustworthiness needs to be restored first. Trust will follow.”

In developing a theory of trust-worthiness for banks, Oliver and De Bruin will navigate the various conflicting interests inherent in financial relationships

– between depositors and borrowers, between bankers and shareholders, and so on – and will chart the complex kinds of interactions needed for successful and trustworthy financial services. To be trustworthy, one must be both able and willing to perform the relevant actions. That is why the research will address key questions of competence and motivation, both of individuals and of organisations.

Oliver and De Bruin are working with a team of two postdoctoral researchers and two PhD students, as well as drawing on the expertise of colleagues in their departments. Using initial results, they designed a 'Philosophy in Business' course for the MBA programmes at Cambridge's Judge Business School, and they have run tailor-made workshops with bankers, from trainees through to boards.

Banks are massively diverse corporate agents. Fine-grained distinctions can be made between retail and investment banking, for example, which are easily conflated in the public mind. Not everyone who works for a bank is a 'bankster' driven by a 'greed is good' mentality, just as not every university staff member is an ivory tower academic.

"Many bank branch employees are trying to serve communities, and are deeply disturbed by 'bad apple' bankers. But their customers tend to tar them with the same broad brush. It's a good question why rogue doctors don't have the same effect. Doctors always top the trust polls, while bankers are now in the gutter with tabloid journalists and politicians," said Oliver.

The manipulation of markets, money laundering, mis-selling of payment protection insurance and interest rate swaps, flawed credit ratings and the subprime mortgage crisis. Where will it end?

Virtues, and how an organisation can embody them, are a cornerstone of the project. Connecting with cutting-edge research on corporate entities and corporate decision-making in philosophy and social science, the project will examine how institutional structures can foster the virtues needed for trustworthiness, such as intellectual honesty and humility, open-mindedness, curiosity and truthfulness.

"The solution can sometimes be as simple as putting the right people in the right place, but typically it is not that simple," said De Bruin, "Organisational change may well be needed, such as rotational policies, in which employees are shifted around to maintain objectivity in their client relationships."

Oliver and De Bruin are keen to emphasise that their work is not a simple one-way transfer of knowledge from academia to the 'real world'. "Philosophers and economists have increased our understanding of 'virtue management', but there are still many open questions. Answering them requires collaboration not only with other disciplines, but also with the banking world itself. Sharing ideas with bankers often leads to reciprocal illumination, which benefits all parties."

One of the project's outcomes will be a 'financial citizenship' initiative. Rather than try to teach people about complex financial products, this will focus on empowering citizens through identifying virtues that help them cope with conflicting financial information. A web-based interactive module will enable prospective clients to test whether they are critical and sober-minded enough to see through the marketing tricks used to sell financial products.

"Where it once stood for cautious financial advice and a firm handshake, the word 'banker' has become slang for a 'greed merchant' who gambles other people's money in rigged games so they alone get rich," said Oliver. "'Trust me, I'm a banker!' is now a well-worn joke. We want to investigate how it can be made good advice."

Left to right
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Professor Boudewijn de Bruin
University of Groningen

And now, the volcano forecast

Scientists are using volcanic gases to understand how volcanoes work, and as the basis of a hazard-warning forecast system.

When the USA's Mount St Helens erupted in 1980, just two months after showing signs of reawakening, its blast was equivalent to 1,600 times the energy of the atomic bomb dropped on Hiroshima. It remains the most economically destructive volcanic event in the USA's history.

When Eyjafjallajökull erupted in 2010 in Iceland, the ash cloud it emitted stranded around half of the world's air traffic, with an estimated global economic cost of US $5 billion. Now magma is on the move again, this time under and beyond Iceland's Bárðarbunga volcano. At the time of writing, the volume of magma was already more than twice the size of Eyjafjallajökull's, and a team of scientists (see page of 4 this issue) has been continuously monitoring its progress.

Volcanoes are the vents through which our planet exhales. Yet, not all volcanoes experience spectacular releases of energy, or even erupt at all: of the 500 or so volcanoes that are currently active worldwide, 20 might be expected to erupt in any one year. But, when volcanoes do erupt, they can cause almost total destruction in the immediate vicinity and the ash clouds they release can affect areas thousands of kilometres away.

> Volcanoes are the vents through which our planet exhales

Fortunately, the ability to monitor volcanoes has dramatically improved in recent years, thanks in part to the work of scientists like Dr Marie Edmonds in Cambridge's Department of Earth Sciences.

Studying the behaviour of volcanoes such as Soufrière Hills in Montserrat, which caused the displacement of two-thirds of the island's population (over 8,000 people) when it erupted in 1995, Edmonds and colleagues have accumulated huge datasets on everything from the type and quantity of gas belched from volcanoes, to the bulging and deformation of the volcanoes' shape, to the altitude and quantity of ash thrown up into the stratosphere.

"About 600 million people live close enough to an active volcano to have their lives disturbed or threatened, so there's a clear need for hazard assessment," Edmonds said. "We knew that gas monitoring data could be essential for this, but monitoring depended on the use of cumbersome instruments that had to be driven around the crater's edge."

In the early 2000s, with funding from the Natural Environment Research Council (NERC), she and Dr Clive Oppenheimer from the Department of Geography developed a new gas sensor – one that is cheap, miniaturised and can be left long term on the volcano, relaying the data back to the observatory by radio modem. Today, sensors like these are used by scientists worldwide for monitoring volcanoes.

All Images
Soufrière Hills, Montserrat

"Previous studies had shown that changes in the emission rate of gases correlated with volcanic activity but, because we have such a long dataset, we began to see another pattern emerging," said Edmonds. "What you see at the volcano surface is really only the end part of the story."

The intense temperatures and pressures deep in the earth find release through fissures and cracks, which carry dissolved gases such as carbon dioxide (CO_2), sulphur dioxide (SO_2), hydrogen chloride (HCl) and steam up through the mantle to the crust.

As the magma begins its journey to the surface, the pressure lowers and dissolved gases form tiny bubbles, which start to expand. Close to the surface, the expansion can be so great that it fuels an explosive burst of lava, shooting volcanic gases tens of kilometres into the earth's atmosphere.

Because each species of gas dissolves at different pressures, the scientists can measure what is released at the surface and use this to work out the depth at which the gases separated from the magma to form bubbles. "The gases are like messages that tell you how the volcano is 'plumbed' and what shape that plumbing is in," explained Edmonds.

"One intriguing pattern to emerge in Soufrière Hills is that the time series for the magma eruption and that for the SO_2 gas eruption are completely unrelated to one another. There have been three big episodes of lava extrusion in the past 15 years and, although HCl flux seems to be a proxy for eruption rate, SO_2 emission is uncoupled from what is happening in the eruption. We think the SO_2 flux is telling us about something much deeper in the system."

When these results were combined with a study of the rocks spewed from the volcano, Edmonds and colleagues began to piece together an idea of the physics and chemistry happening within.

They believe that a hot magnesium- and iron-rich 'mafic' magma is intruding from depth into the shallower magma chamber where it meets a silica- and crystal-rich 'andesite' magma that forms the main part of the eruption. However, it is the gas-rich mafic magma that Edmonds and colleagues believe triggers and fuels the eruption, and it is this that surface SO_2 levels are a proxy for.

"This is far from the traditional view of how a magma chamber works," said Edmonds. "It was thought to be balloon-like but now we think it's vertically protracted, with different types of magma at different levels."

"The surface SO_2 is telling us about long-scale processes, of the order of months to years," explained Edmonds. "Even though there may be no evidence of lava at the summit, if SO_2 is still outgassing then there's potential for the eruption to resume. We can to an extent use it to forecast a volcanic eruption."

Recently, Edmonds and colleagues joined forces with researchers at other universities to understand how best to monitor volcanoes and earthquakes in two new NERC-funded projects. The £2.8 million Centre for the Observation and Modelling of Earthquakes, Volcanoes and Tectonics (COMET+) programme run by the University of Leeds will provide new understanding of geohazards to underpin national risk capabilities; and the £3.7 million RiftVolc project will create a long-range eruptive forecast for the largely uncharted volcanoes in the East African Rift Valley.

For Soufrière Hills, monitoring is providing a key input to the risk assessments by the UK government's Scientific Advisory Committee for Montserrat, a British Overseas Territory. "All the surface signs indicate the volcanic activity is decaying away but, from the SO_2 emissions, the volcano remains active at depth. We think there's a huge magma reservoir – tens of cubic kilometres beneath the island, much bigger than the island itself. We know from looking at older ash deposits on the island that this volcano is capable of much larger eruptions than we have seen in recent years, perhaps even as large as the Mount St Helens blast."

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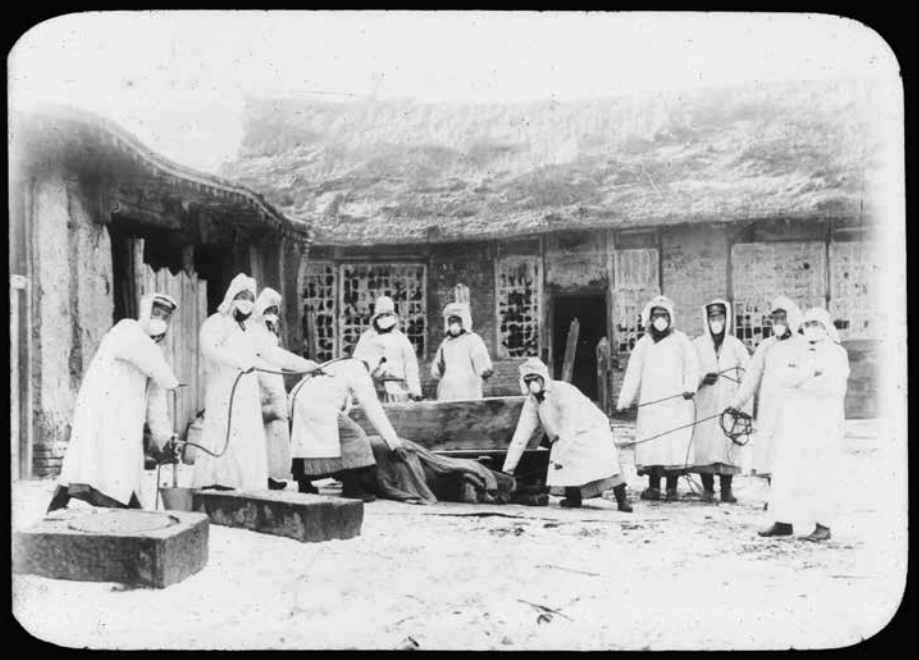
Visions of plague



Credit: Harvard Medical Library in the Francis A. Countway Library of Medicine

A new research project is compiling the largest database of plague imagery ever amassed, focusing on a pandemic that peaked in the early 20th century and continues to this day.

We are in the midst of the worst Ebola outbreak known in human history. Our screens are filled with nightmarish yet strangely familiar imagery. Men in space-age protective suits, lugging wrapped-up bodies over to hastily dug pits. Clinical tents in poor yet exotic locations, gleaming incongruously. Bodies in the streets.

As Ebola continues its trail of death and terror, many will be unaware that we also continue to live with another killer – plague. The most recent pandemic (the third) started in rural China in 1855 but exploded when it reached Hong Kong in 1894, sweeping the world and killing over 12 million people. Although it has not been considered an active threat since 1959, recent cases of plague have occurred in Bolivia, China, Madagascar and the USA.

Dr Christos Lynteris is a social anthropologist based at the Centre for Research in the Arts, Social Sciences and Humanities (CRASSH). During work on plague among marmots on the Chinese–Russian border, Lynteris started to consider how plague is represented, how knowledge about plague is captured and how we interact with what we see when we encounter the traits of plague.

The most recent pandemic started in rural China in 1855 but exploded when it reached Hong Kong in 1894, sweeping the world and killing over 12 million people

Image
Plague imagery

"The third pandemic was born around the same time as modern photographic techniques, and the ability to capture and transmit images of the third plague pandemic transformed public consciousness. It opened up an era where the meaning of health emergencies is publicly negotiated, rather than predetermined by any single scientific or governmental authority."

Last year, he was awarded a European Research Council grant to find, collate and analyse the largest database of plague imagery in history; as the only exhaustive visual record of any infectious disease epidemic and its impact on social life and thought in the modern era, it will be an invaluable resource to historians, anthropologists and epidemiologists alike.

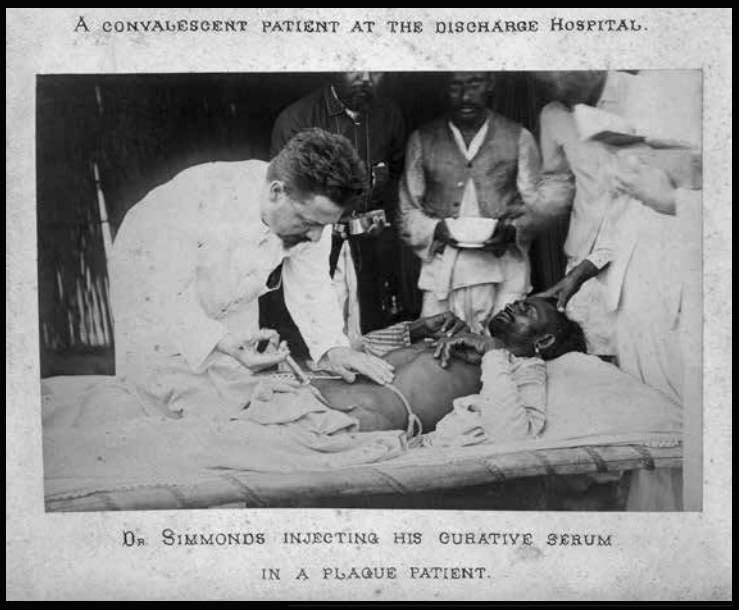
Tracking the images down takes painstaking investigative work for Lynteris and his team (Lukas Engelmann, Nick Evans and Branwyn Poleykett), sifting through photographic remnants of the old colonial powers to pick out the diseased, the dying, the depictions of human *Yersinia pestis* infection. "Many of the images are not held in the places where outbreaks occurred. An archive in Alabama might hold a hundred images of the plague in North China because that's where the missionaries were from. Foreign doctors, missionaries, reporters go to all corners of the planet to work with plague epidemics; it can be a tricky web to untangle."

He describes the imagery as a "strange combination of journalistic war reporting, crime scene photography and medical imagery." Some of it is so graphic and distressing that part of the grant stipulates the digital archive must be kept in a locked room at all times, the 'plague room' as Lynteris cheerfully refers to it. Entering anywhere with such a moniker is slightly unnerving.

"OK, this next one really isn't very pretty," said Lynteris, showing one of the thousands of images they have already collected. Lynteris probably says this a lot these days. The photo, taken in Madagascar in 1899, feels familiar. The tents. The pits. The suited spacemen. If not for the sepia, this could be West Africa in 2014.

"There is a clear visual paradigm of plague inherited from imperial and colonial history that is emerging as we gather more and more images, an expression of diseased environments we still live with," explained Lynteris.

"The visual paradigm in the Madagascar photo is replicated throughout the third pandemic and in other outbreaks since,



Credit: All images on this page, Wellcome Images

even over a century later, despite the fact that the medical paradigm has completely shifted – we know far more about infectious diseases now than in 1899, so why are we seeing the same imagery? By taking the aesthetic regime from a hundred years ago and replicating it today you are inadvertently replicating a long surpassed medical model."

Asked whether governments and media are propagating these portrayals because this is what people expect, even need to see, Lynteris said: "I'm not sure, but something is not right here. It's the components and rationale behind these visual paradigms that we will explore."

Not all the imagery is gruesome. Some resemble forensic architectural photos. "When the plague hit the USA, investigators would meticulously photograph every house in the infected area – cellars, floors, beams – looking for clues as to the conditions that facilitate plague."

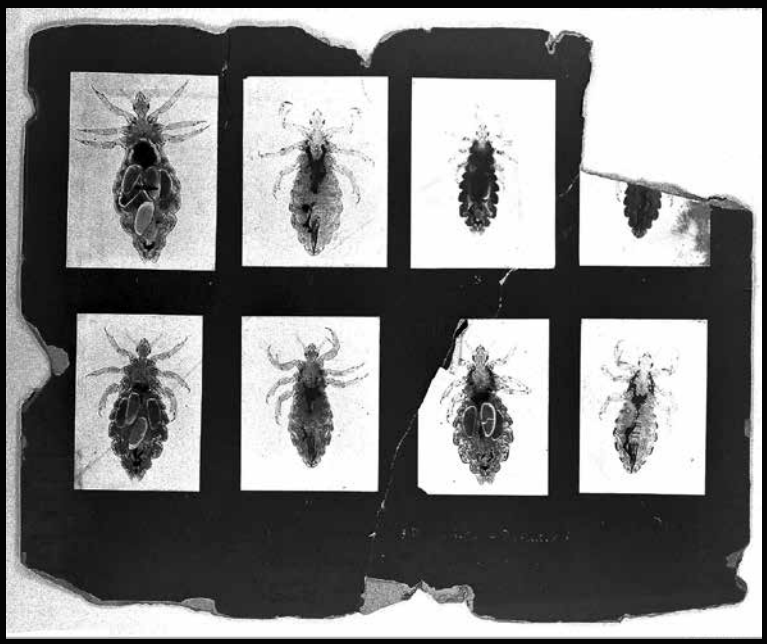
In another set of images from an outbreak in Manchuria in 1911 that killed 60,000, Lynteris highlights an imperialist propaganda war being fought out in the plague depictions. Russia and China were trying to claim providence of the area, with both determined to prove that it was they who were the most scientific and could tame the plague.

"The Chinese were trying to present an image of high science and hygienic modernity, full of medical teams with microscopes and charts. They depicted plague as an urban planning problem that can be scoured by fire." There are many pictures of burning houses, but not a single human body.

The Russians went a different way ("it's a horror show"). The images are entirely militaristic, as if an army invaded a land where everyone was already dead. The aim was to show that the Chinese had no control, that death was rife and unstoppable without Russian force: "it was intended to scare, show oriental barbarity with dogs eating corpses and exposed plague pits." Images like these are why the 'plague room' is kept locked.

The team has had to create a language of plague to make sure the database is fully searchable, and aim to have it live and open access by the time the project finishes in 2018. They are working not just with other anthropologists and medical historians but with epidemiologists. Should fundamental questions about plague arise among life scientists, the archive might hold clues as to the history of certain assumptions.

Most importantly, the team is focusing on the relationship between the ethics and aesthetics of plague photography. "The implications of this in the age of social media are immense. How do we capture an outbreak like Ebola with our cameras? How does this reflect our responsibility towards the victims, but also in terms of global health?" It's alarming, Lynteris says, that there seems to be no difference between how we depict outbreaks today and how we did a hundred years ago. "In the post-colonial world, epidemic photography is still stubbornly colonial."



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Where there's muck there's aluminium (if not brass)

Technology developed in Cambridge lies at the heart of a commercial process that can turn toothpaste tubes and drinks pouches into both aluminium and fuel in just three minutes.

It started with a bacon roll and a microwave oven, and now it's poised to transform the recycling of a packaging material that has been as unrecyclable as it is useful.

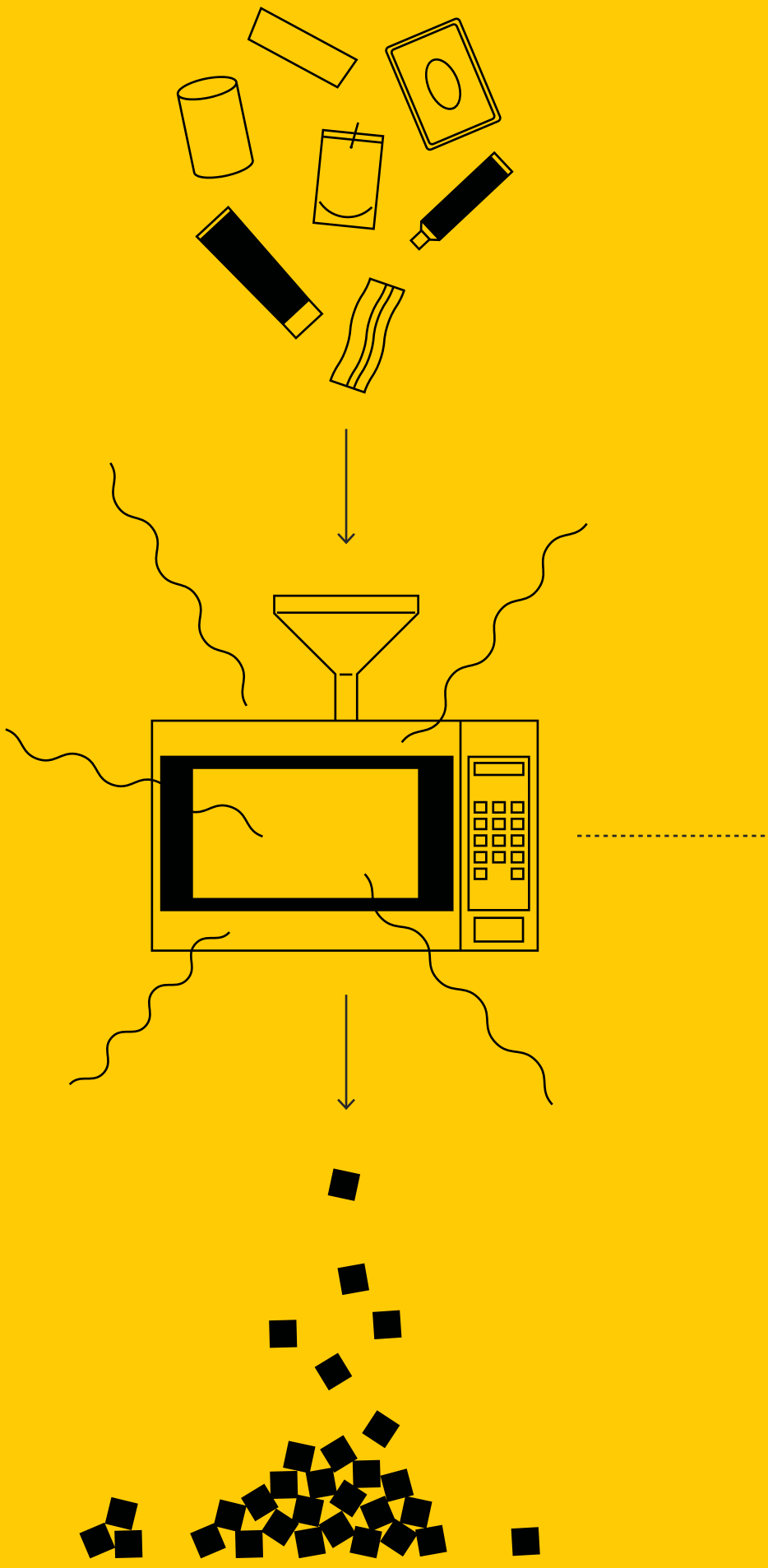
The bacon roll, as the story goes, was microwaved for so long it turned into a charred mass of carbon that began to glow red-hot. What was happening was an intense heating process called microwave-induced pyrolysis.

On hearing about the 'over-microwaved' bacon roll from an acquaintance, chemical engineers Professor Howard Chase and Dr Carlos Ludlow-Palafox (a PhD student at the time) wondered whether the process could be exploited to recover useful materials from packaging wastes.

Particulate carbon is an efficient absorber of microwaves and can transfer this thermal energy to adjacent materials. If the adjacent material is organic, such as plastic or paper, it breaks apart (or pyrolyses) into smaller pieces; if the material is a metal attached to the plastic or paper, the metal can be recovered in a clean form after the attached organics are pyrolysed.

Fifteen years later, and the technology they developed is now being used in a commercial-scale plant designed, built and operated by Cambridge spin-out Enval Limited. Founded by Ludlow-Palafox, with Chase as R&D Director, Enval is using the plant to demonstrate the capabilities and economics of the process to investors and waste handlers.

Enval has focused on plastic–aluminium laminate packaging. Prized by manufacturers for its lightness, cheapness and ability to protect the contents from light and air, the packaging is commonly used for food, drink, toothpaste, pet food and cosmetic products.



They placed a pile of particulate carbon and some shredded laminated packaging inside a conventional 1.2 kW kitchen microwave… when they opened the door, the laminated material had been separated into clean aluminium flakes

However, the combination of plastic and aluminium in the packaging presents a technical recycling challenge that until now has been unsolved; instead, items packaged like this contribute to the millions of tonnes of rubbish disposed of in landfill each year. For the brands who package their consumer goods this way, the 'recyclable logo' on the packaging, and the sustainability credentials that go with this, has been all-elusive.

"We have carried out a life-cycle assessment of the packaging and it's still environmentally better to use these laminates even though they are not recyclable, just because so little materials and energy goes into making and transporting them compared with alternatives like glassware and cans," said Ludlow-Palafox.

"There is no real drive to replace them and their market use is increasing by about 10–15% every year. In the UK, roughly 160,000 tonnes of laminates are used per year for packaging, which means at least 16,000 tonnes of aluminium is going into the ground. Just imagine if we could routinely recycle this."

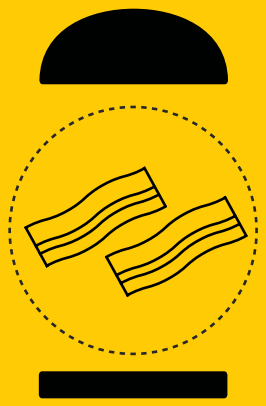
The solution he and Chase developed with funding from the Engineering and Physical Sciences Research Council started in a relatively simple way: they placed a pile of particulate carbon and some shredded laminated packaging inside a conventional 1.2 kW kitchen microwave, replaced the air inside the oven with nitrogen and turned the microwave up to full power until the temperature increased to about 600°C.

When they opened the door two minutes later, the laminated material had been separated into clean aluminium flakes and hydrocarbon gases and oil.

The basic chemistry is still the same in the commercial-scale plant but the oven is now 150 kW and large enough to be housed in a 100 m^2 industrial unit. It takes just three minutes to convert waste into aluminium for smelting, and hydrocarbons for fuel, and with no toxic emissions.

Now fully commissioned, the plant can recycle up to 2,000 tonnes of packaging a year – which, say the researchers, is roughly the amount handled by regional waste handlers – and it generates enough energy to run itself. Enval now has an arrangement with manufacturers of plastic–aluminium laminates to recycle their industrial scrap at less than what they would have spent on sending it to landfill.

The researchers have, in effect, turned into commercial waste handlers – something they would never have imagined back in the 1990s. "While we were getting into the world of laminates it didn't cross our minds to start a company… we just wanted the process to become a reality," said Ludlow-Palafox. "In the end, the investors [Cambridge Capital Group and Cambridge Angels] said there is no one else who knows the process as well as you, you might as well do it!"



"We knew that the patented technology offered a genuine recycling route for this type of packaging but that the waste industry can be slow to take on new technology – the margins in environmental services are small, and we needed a working, full commercial-scale plant to convince them that the process was viable," said Chase, who estimates that a plant like theirs would pay for itself within three years. "In parallel, we were being contacted by the brands who use the packaging, asking how they could help."

The commercial-scale plant is part-funded by Nestlé and Kraft Foods/ Mondelez International.

"It was a chicken and egg situation," said Ludlow-Palafox. "No one is going to buy this technology unless this type of waste is separated for recycling, but the waste wasn't going to be separated because there has been no process to recycle it. We had to break that negative loop somehow. Now we have the commercial-scale plant, we can show waste handlers the benefits and encourage local authorities to implement a selective collecting system."

Meanwhile, the scientists are keeping an eye on future recycling prospects. Research into the microwave pyrolysis of different types of wastes continues in Chase's group in the Department of Chemical Engineering and Biotechnology. "It's crucial that we continue to look for new opportunities for recycling valuable materials while simultaneously eliminating the need to send wastes to landfill or incineration.

"We've demonstrated that a lot of troublesome waste materials can be pyrolysed using our microwave technology but it's not always economically sensible to do it; the challenge now is to identify which processes are likely to be commercially viable, and which of those will attract the necessary investment funding to bring them into commercial reality. This is a business sector that is comparatively unfamiliar to most investors who regularly commit to innovation in other areas. By demonstrating the societal and economic benefits of green technologies, we hope to secure the necessary investment to transform innovation into successful commercial practice."

Left to right
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Credit: With permission of the National Gallery

Fancy pants & the fashion police

Men's fashion didn't come cheap in 16th-century Italy. Nor did it go down well with the authorities. PhD student Giulia Galastro is researching the level of opulence that could be paraded in public – and how the dandies of the day neatly sidestepped the rules.

On 15 September 1595, Salvagio de Aste was spotted breaking the law in Genoa. The record in the city's state archives describes with remarkable precision what he was wearing as he strolled through the square of San Siro. He must have cut a dashing figure. He sported "an embroidered cap, a silk doublet of many colours with gold buttons on the sleeves, two rings with white stones on his fingers, a jerkin and embroidered hose in black silk."

The detail with which Salvagio's attire was noted is no accident: his showy and costly clothing was his crime. His costume had fallen foul of Genoa's Magistrato delle Pompe, whose role it was to enforce the

Image
Painting of Lord John Stuart and his brother, Lord Bernard Stuart, by Anthony van Dyck

A whole outfit in silk velvet, embroidered with precious metal threads, could come close to the price of a sports car today

sumptuary laws that regulated what men and women could wear. Patrolling the streets and squares of the bustling city as arbiters of the level of ostentation that was deemed appropriate, the sumptuary magistrates were quite simply the fashion police.

The role of these magistrates, and their (largely unsuccessful) attempts to moderate excessive spending, is one strand of research into clothing and society in early modern Genoa being carried out by Giulia Galastro, a PhD candidate in the Faculty of History working with Dr Mary Laven. Sumptuary laws restricted the use of the luxurious textiles for which Genoa was famous, along with expensive decoration such as gold and silver embroidery, jewellery and 'ostentatious' modes of transport.

Italy wasn't alone in having sumptuary laws – the obsession with legislating against costly clothes spread across Europe during the Middle Ages. The aims of the laws are subject to some debate. Their wording suggests concern that luxury goods could morally damage those who consumed them, that fashion's transitory nature stoked an acquisitive lust for new goods.

Financial considerations too were at play. A 15th-century Genoese law bemoaned "a great quantity of money which is kept dead and wrapped up in clothing and jewels, [and] if converted into trade might bring great return and profits." Some historians have argued that the laws were an indirect tax on wealth, working on the tacit assumption that the rich would be prepared to pay to get around them.

"Part of the problem is that not much evidence for how the laws were enforced has been preserved, so it's difficult to know how – and whether – they worked in practice. That's what makes the Genoese sumptuary records so special. The rare survival of notes kept by the sumptuary magistrates give us a glimpse of the laws in action, and of clothes in use. We can begin to build up a picture of who was wearing what, when and where," said Galastro. The records suggest that residents of Genoa routinely ignored the sumptuary laws. In the four years from 1594 to 1598, the magistrates recorded more than 560 contraventions of the regulations.

The foppish Salvagio was among the repeat offenders. Three days after being admonished on 15 September 1595, he was back in San Siro – wearing exactly the same outfit. On 5 November, he was there again, wearing a leather jerkin impregnated with musk.

The sumptuary magistrates were caught up in a game of catch-me-if-you-can as Genoa's dandies defied and subverted the rules. The feckless Salvagio broke the law at least a further four times, suggesting that whatever fine was imposed was no deterrent to a man determined to strut his stuff.

"It is likely that any fines imposed were modest in comparison with the cost of the offending garments. A whole outfit in silk velvet, embroidered with precious metal threads, could come close to the price of a sports car today: if you could afford to buy the clothes, you could afford to pay the fine – or the bribe," said Galastro.

"Contrary to widely held beliefs, male offenders outnumber females. In terms of overall sumptuary offences, there are 289 men to 242 women. If we focus on offences concerning dress, however, the disparity is more striking: 269 men to 99 women. In other words, there were almost three times as many men breaking the law on clothing as women."

Historians have often presumed that, where sumptuary laws mention men at all, it is for dressing too femininely, but Galastro's research suggests something different. "It's interesting that the majority of the offences relate to an outfit of black silk – taffeta, satin or velvet – ornamented with some sort of precious metal stitching or with lace. Black was a clear status symbol in Renaissance culture because it was one of the most difficult dyes to fix effectively," said Galastro.

"If you pair the sumptuary records with literary sources it seems that what was disquieting to the sumptuary magistrates in Genoa was a particular form of vaunting, flaunting masculine dress."

In his 1620 commentary on the *Characters of Theophrastus*, the Genoese writer Ansaldo Ceba describes the effrontery of the young man who will "when he is wearing breeches *alla Spagnola*, or an embroidered doublet, circulate around the city so sedulously that you can't help bumping into him in church, in the square, or on the corner… You needn't think of leaving until you have admired him from head to toe. Indeed he will compel you to do so, now by opening his cloak, now by planting himself in front of you like a bulwark."

Infringements of the sumptuary laws weren't confined to the elite: artisans too were under scrutiny. Some were caught by the sumptuary magistrates while making luxury clothes. On 20 May 1595, the wife of Gioannetino the cheese-maker was spotted sitting on her doorstep sewing a man's silk shirt, dyed in costly crimson, with gold and silver braids three fingers' thick.

"Some 60% of the population were involved in the production of textiles and clothing – from the women employed to unwind silk filament from cocoons through the dyers and weavers in their workshops to the hundreds of tailors and seamstresses," said Galastro.

It was an era when people had a hands-on relationship with textiles, choosing and purchasing fabrics in consultation with their tailors and eagerly awaiting the arrival of new textiles and trimmings. The vocabulary of fabrics and fashion was fabulously diverse – colours such as 'incarnadine' (the red of raw flesh) – most of these words lost to us today. As Galastro's research is showing, what you wore, and how you wore it, was a matter of deep significance.

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Lifelong learning and the plastic brain

Our brains are plastic. They continually remould neural connections as we learn, experience and adapt. Now researchers are asking if new understanding of these processes can help us train our brains.

When a group of experimental psychologists moved into their new lab space in Cambridge earlier this year, they took a somewhat unconventional approach to refurbishing their tea room: they had the walls tiled with the Café Wall Illusion.

The illusion, so-named after it was spotted on the wall of a Bristol café in the 1970s, is a much-debated geometrical trick of the eye and brain in which perfectly parallel lines of black and white tiles appear wedge-shaped and sloped.

It's also an excellent demonstration of how the brain interprets the world in a way that moves beyond what the input is from the eye, as one of the experimental psychologists, Professor Zoe Kourtzi, explained. "In interpreting the world around us, our brains are challenged by a plethora of information. The brain is thought to integrate information from multiple sources and solve the puzzle of perception by taking into account not only the signals registered by the sensory organs but also their context in space and time.

"In the Café Wall Illusion, the brain takes into account the surrounding tiles, but it also relies on our previous knowledge acquired through training and experience when interpreting a new situation."

From the day we are born, neurons in the brain start to make connections that combine what we can see, hear, taste, touch and smell with our experiences and memories. Neuroscientists refer to the brain's 'plasticity' in explaining this ability to restructure and learn new things, continually building on previous patterns of neuronal interactions.

To unravel the mechanisms that underlie how brains learn, Kourtzi's team is looking at how brains recognise objects in a cluttered scene. "This aspect is vital for successful interactions in our complex environments," she explained. "It's how we recognise a face in a crowd or a landmark during navigation."

It's an excellent demonstration of how the brain interprets the world in a way that moves beyond what the input is from the eye

Visual perception is also highly trainable. The brain can use previous experience of similar cues to be quicker at identifying the image from the 'noise' – the proverbial needle from the haystack.

But although neuroscientists recognise that this type of brain plasticity is fundamental to our ability to cope with continually changing settings at home, school, work and play, little is known about how we can stimulate our brain to enhance this learning process, right across the life span.

"The process of 'learning to learn' is at the core of flexible human behaviours," explained Kourtzi. "It underpins how children acquire literacy and numeracy, and how adults develop work-related skills later in life."

One of the important determinants her

Images
The Café Wall Illusion – tiles that trick the eye and the brain

Credit: funstuffcafe.com/cafe-wall-illusion

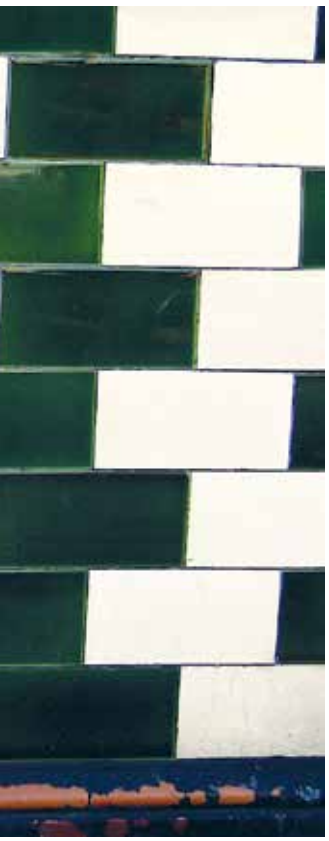
team has discovered is that being able to multi-task is better than being able to memorise.

"The faster learners are those who can attend to multiple things at the same time and recruit areas of the brain that are involved in attention," she explained. "Those who are slower at learning try to memorise, as we can see from greater activity in the parts of the brain connected with memory."

"So, in fact, being able to do the sort of multi-tasking required when interacting in busy environments or playing video games – which requires the processing of multiple streams of information – can improve your ability to learn."

She also finds that age doesn't matter: "what seems to matter is your strategy in life – so if older people have really good attentive abilities they can learn as fast as younger people."

This has important implications for an ageing society. In the UK, there are now more people over State Pension age than there are children. The UK's Office for National Statistics predicts that, by 2020, people over 50 will make up almost a third of the workforce and almost half of the adult population. The average life expectancy for a man in the UK will have risen from 65 years in 1951 to 91 years by 2050. Older age has become an increasingly active phase of people's lives, one in which re-training and cognitive resilience is increasingly sought after.



Credit: Tony Kerr on Flickr

Kourtzi and colleagues are using functional magnetic resonance imaging to detect when areas of the brain are activated in response to a sensory input and how these circuits change with learning and experience. While at the University of Birmingham, she showed that the visual recognition abilities of young and older adults can be enhanced by training, but that the different age groups use different neural circuits to do this.

Young adults use anterior brain centres that are often used in perceptual decisions, where sensory information is evaluated for a decision to be made; older adults, by contrast, use the posterior part of the brain, which is in charge of the ability to attend and select a target from irrelevant clutter. "The clear implication of this is that training programmes need to be geared for age," said Kourtzi.

Crucially, what she also observed is that some people benefit from training more than others: "although it's well known that practice makes perfect, some people are better at learning and may benefit more from particular interventions than others. But to determine how and why, we need to go beyond biological factors, like cognition or genetics, to look at social factors: what is it about the way a particular individual has learned to approach learning in their social setting that might affect their ability to learn?"

This multidisciplinary approach to understanding learning lies at the heart of her work. She leads the European-Union-funded Adaptive Brain Computations project, which brings together behavioural scientists, computer scientists, pharmacologists and neuroscientists across eight European universities, plus industrial partners, to understand and test how learning happens.

"In our work, there's a strong element of translating our findings into practical applications, so creating training programmes that are age appropriate is our ultimate goal," she added.

"The reason we like the Café Wall Illusion so much is because tricks of visual perception tell us that the brain can see things in a different way to the input. How the brain does this is influenced by context, just as the way we interpret our environment is influenced by learning and previous experience."

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Things Treasured possessions

Images
Some of the 'treasured possessions'

A collection of 'possessions' shows us how people treasured beautiful things before mass production and a disposable culture irrevocably changed our relationship with the material world.

They are not the most practical footwear. They are not even fitted for the left and right foot. But these 18th-century silk shoes, with their pointed toes and thick curving heels, were designed with fashion not function in mind. Cherished, shown off, perhaps bequeathed, they would have been treasured by their stylish owner to a degree that might be hard to fathom in the context of today's mass consumerism.

Three Cambridge historians – Dr Mary Laven, Professor Ulinka Rublack and Dr Melissa Calaresu – have teamed up with Dr Vicky Avery, Keeper of Applied Arts at The Fitzwilliam Museum, to explore possession from the Renaissance to the Enlightenment. "Our goal is to shed light on the meaning of objects to their owners in an age of expanding possibilities, new technologies and global exchange," explained Laven.

"Ever since beautiful and engaging objects were first created, people have wanted to possess and cherish them, making their 'favourite things' part of their lives. Possessions not only define us, they also say something about our personal histories."

Their research will culminate in a six-month exhibition that will open in March 2015 and feature more than 250 of the Museum's treasures – among them a mourning seal 'Sacred to the Memory of an Adopted Child', an exquisite tortoiseshell snuffbox and a Delftware bird cage – many of which are rarely displayed.

"The exhibition juxtaposes iconic artefacts with unfamiliar, quirky objects that are usually passed over," Laven added. "Each of these objects had significance… It's easy to forget these secret histories when you pass through a museum, viewing objects in isolation."

The collections at The Fitzwilliam Museum explore world history and art from antiquity to the present day.

www.fitzmuseum.cam.ac.uk

Image
Yellow silk taffeta shoes, made in 1749 in England

Credit: All images, The Fitzwilliam Museum

Credit: Jenny Nichols

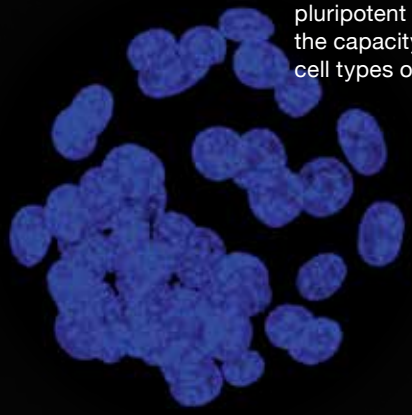
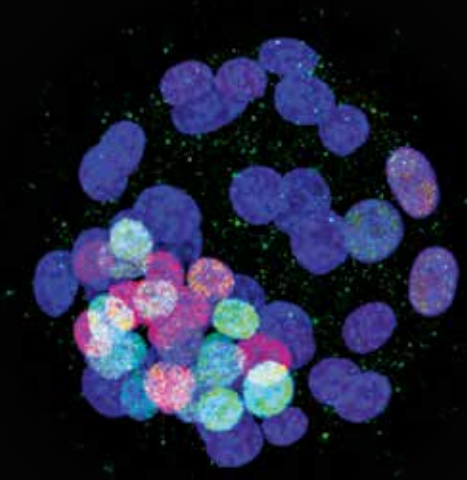


Image
A mouse blastocyst at the pluripotent stage, when cells gain the capacity to generate all of the cell types of the subsequent adult

The 'Ultimate' Stem Cell



Stem cell biologists are a step closer to identifying what some have called the 'Higgs Boson' of the field: the moment in the developing human embryo when everything is possible.

In the earliest moments of a mammal's life, the developing ball of cells formed shortly after fertilisation 'does as mother says' – it follows a course that has been pre-programmed in the egg by the mother.

Extraordinary as this is, what happens then is even more remarkable. Just before implantation in the uterus, the ball of cells, called a blastocyst, gains the capacity to generate all of the cell types of the subsequent adult – a feature called pluripotency. It is at this moment when everything is possible, when the history of the previous generation has been wiped clean and when the embryo begins its unique course of development.

But, although these 'naive' stem cells have been isolated in mice – and mouse cells at a later stage of development can be manipulated to take them back to full naivety – the same has not been convincingly accomplished for humans.

In fact, in an assessment earlier this year, Cambridge researchers Professor Roger Pedersen and PhD student Victoria Mascetti concluded that the existence of naive human stem cells required confirmation by other stem cell research groups: "Like Higgs' Boson to the field of particle physics," they explained, naivety in human stem cells "was predicted from considerations of symmetry and conservation, [but] we are yet to unlock its potential."

Now researchers led by the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute have

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It is at this moment when everything is possible

managed to induce a ground state by rewiring the genetic circuitry in human embryonic stem (ES) cells and in adult cells that have been induced into a pluripotent state. Their 'reset cells' share many of the characteristics of authentic naive ES cells isolated from mice, suggesting that they represent the earliest stage of development.

"Capturing ES cells is like stopping the developmental clock at the precise moment before they begin to turn into distinct cells and tissues," explained Professor Austin Smith, Director of the Institute, who co-authored a recent paper on the research. "Scientists have perfected a reliable way of doing this with mouse cells, but human cells have proved more difficult to arrest. They show subtle differences between the individual cells. It's as if the developmental clock has not stopped at the same time and some cells are a few minutes ahead of the others."

He added: "Truly naive human ES cell lines would not only help answer fundamental questions about how we are made, and be useful for drug screening and tissue therapy, but they would also provide a benchmark against which other types of stem cells could be measured in terms of their effectiveness in stem cell therapy and regenerative medicine."

Over the past 20 years, research groups led by Smith and Dr Jenny Nichols at the Institute have made a major contribution both to understanding the early stages of mouse development and to determining how to make stable mouse stem cell lines more efficiently. They know enough to realise that it's very different in humans, as Nichols explained: "Pluripotent cells that seem very similar to the mouse naive pluripotent cells appear in the human blastocyst before implantation but we don't know what happens to those cells for the following week of development. We can only make assumptions based on what happens in the mouse."

Their recent study, published in September 2014 in the journal *Cell*, proves that they are closer to capturing naive pluripotency in humans: "We know almost all we need to know about the molecular requirements for creating the ground state in mice," Smith said. "We have identified the genes and growth factors involved and, thanks to a collaboration with Microsoft Research, we can now computationally model the control circuitry in mouse cells. It's reinforced our view that we understand enough to know what to look for in humans and which combinations of genes to focus on. It's now only a matter of time."

And when that happens, work will begin on comparing them with other sources of stem cells, through collaborations such as the PluriMes project that Smith coordinates, a newly launched consortium of 10 European partners focused on directing pluripotent stem cells to become bone and muscle, and a collaboration with orthopaedic surgeon Professor Andrew McCaskie (see panel).

Could naive human ES cells be the stem cell of choice for tissue therapy? "We don't yet know," said Smith. "These cells would offer the hope of having a broader and more consistent ability to differentiate into a range of cell types because they are at an earlier stage of development. But it's also entirely possible that current stem cells are good enough for some applications. The point is, we needed these new stem cells in order to find out what is best."

Lengthening the journey to joint replacement

Translating scientific discoveries to the clinic can be a major challenge, which is why Austin Smith and orthopaedic surgeon Andrew McCaskie are working together on research that could radically change the way we treat conditions like osteoarthritis.

"Osteoarthritis is a rapidly growing health problem, with over 8 million people affected in the UK," explained Professor Andrew McCaskie from the Department of Surgery. "The conventional approach is to treat the condition when the joint is extensively damaged by using a joint replacement. We want to treat the condition at an earlier stage using repair and regenerative techniques to prolong the use of the patient's own joint and therefore defer joint replacement."

McCaskie is Director of the Arthritis Research UK Tissue Engineering Centre, a national multicentre collaboration focused on both cell and cell-free approaches to regenerative therapies in osteoarthritis. He also leads another multicentre consortium (Smart Step) that aims to explore ways to stimulate the patient's own repair mechanisms by targeting their cell populations. Smart Step is funded through the UK Regenerative Medicine Platform by the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council and Medical Research Council.

"A pivotal part of responsible translation to the patient is a clear understanding of relevant adult cell populations," he added. "Austin's expertise in fundamental stem cell biology will allow new insights into how these cells work, which may then influence their use in safe and evidence-based therapy."

McCaskie is also developing musculoskeletal science in Cambridge in a more general way: "The musculoskeletal system is uniquely reliant on linking biological form to mechanical function. We have started a networking process to develop Cambridge Musculoskeletal Science and facilitate interaction between physical and biological sciences, technology and clinical medicine, to enhance bench to bedside interdisciplinary research, with the ultimate aim of transforming patient care."

Orchestral manoeuvres: *multiple sclerosis faces the music*

Like conducting an errant orchestra to play together, researchers are guiding processes that go awry in multiple sclerosis to repair themselves.

The conductor walks to the stand and takes his place in front of the orchestra. He raises his baton and, with a dramatic flourish, one hundred individuals come to life. From nowhere, the stillness becomes a beautiful harmony as each member takes their part in a complex symphony.

Consider the workings and structure of the human brain – our most complicated organ – in terms of this orchestra

Consider the workings and structure of the human brain – our most complicated organ – in terms of this orchestra. When it works, it is capable of something more remarkable than the greatest musical compositions in human history, but when it is affected by a condition such as multiple sclerosis (MS), "the brain's tightly orchestrated biological functions become discordant – the conductor begins to fail at their job and several instruments go out of tune," said Professor Robin Franklin, Head of Translational Science at the Wellcome Trust-Medical Research Council (MRC) Cambridge Stem Cell Institute and Director of the MS Society Cambridge Centre for Myelin Repair.

His research team and those led by other Stem Cell Institute researchers Drs Thóra Káradóttir, Mark Kotter and Stefano Pluchino are each looking at a different aspect of this errant orchestra. They hope that their collective knowledge will one day help 're-tune' the brains of MS patients to self-repair.

In its simplest terms, MS is a disease in which the immune system turns on itself, destroying the oligodendrocytes that make a protective sheath called myelin, which encases nerve fibres. This halts the transmission of neural messages, and eventually leads to nerve fibre damage, resulting in a progressive loss of movement, speech and vision for the 100,000 people in the UK who have MS.

However, the complexities of treating the disease go beyond simply stopping the destruction of myelin, said Franklin: "The myelin damage causes a build-up of debris, which needs removing, and the environment surrounding the cells needs to be conducive to regenerating the sheath. When we think about repairing the damage, we need to be considering several different biological phenomena at the same time."

Although there are drugs available for modifying the early stages of MS – including alemtuzumab (Lemtrada), developed in Cambridge – there are no treatments that regenerate the damaged tissue. Moreover, although the disease evolves over decades, with periods of remission followed by relapses, there is no treatment once patients have reached the progressive stage (estimated to be about 50% of current patients).

Oligodendrocytes – the master manufacturers of myelin – are formed by a type of stem cell in the brain called oligodendrocyte progenitor cells (OPCs), and are responsible for re-wrapping, or remyelinating, the bare axons with myelin in response to injuries or diseases. But this regenerative ability decreases with age and MS. "As the disease progresses, the need for intervention that galvanises the natural healing process becomes ever more important," explained Franklin. "Working with colleagues at the Harvard Stem Cell Institute, we've shown that the effects of age on remyelination are reversible, which gives us some confidence that we can use the brain's own OPCs for myelin regeneration."

However, to understand how to stimulate the brain's own repair mechanisms first requires an understanding of how the brain detects injury and initiates repair.

Thóra Káradóttir believes that one way the brain 'senses' problems are afoot is through the drop in how fast neural messages are passed across the brain. "The difference in speed between an intact neuron and a damaged one can be like comparing the speed of a cheetah to a tortoise," she said. "I'm eavesdropping on the information superhighway by attaching electrodes to neurons and OPCs."

Her findings show that damaged fibres release a molecule called glutamate. "It's their 'cry for help' to OPCs. If it doesn't happen, or if the OPCs don't 'hear', then repair is reduced." She is working with Numedicus, a company that specialises in developing secondary uses for existing drugs, to test drugs that she hopes will be able to amplify this signal and increase the repair process.

Meanwhile, Robin Franklin's team has shown that it's possible to kick-start OPCs, driving the formation of oligodendrocytes and sheath formation, using a drug that targets retinoid X receptor-gamma, a molecule found within OPCs. The results are positive and clinical trials will shortly commence in collaboration with Dr Alasdair Coles from the Department of Clinical Neurosciences and the MRC Centre for Regenerative Medicine at the University of Edinburgh.

What's interesting about the rejuvenation of remyelination is that the treatment primarily affected inflammation in demyelinating lesions, and specifically the recruitment of cells called macrophages. These are the body's 'big eaters' – their role is to search out and gobble up rubbish. "We have identified myelin debris as a potent inhibitor of stem cells. Learning how it is being sensed by stem cells enabled us to overcome this inhibition by using drugs such as ibudilast. A clinical trial to test these effects is currently undergoing preparation," explained Mark Kotter.

Franklin and Kotter's work is representative of an interesting turn in MS research within the field. Increasingly, investigators are looking at how the environment around the damage can be improved to help natural remyelination. "It's a curious paradox," said Franklin. "MS is caused by the immune system but components of the immune system are also key to its recovery."

Stefano Pluchino's team, for instance, has shown that injecting brain stem cells into mice with MS works in a surprising way. Instead of making new oligodendrocytes (or other brain cells), the cells seem to work by re-setting the damaging immune response, creating better conditions for the brain's own stem cells to replace or restore what has been damaged. He is now developing more-efficient stem cells and new drugs, including nanomedicines, to foster the healing of the damaged brain.

They hope that their collective knowledge will one day help 're-tune' the brains of MS patients to self-repair

Given the complex landscape of abnormal activities happening in the MS brain, will combination therapies be the way forward? "Certainly," said Franklin. "Over the next ten years we will see an increased understanding of the fundamental biology in MS, we will identify more targets which may yield effective drugs and we'll have more-refined strategies for running clinical trials. What makes Cambridge rare is the spectrum of skills here – from understanding the fundamental biology of myelin repair through to clinical trials."

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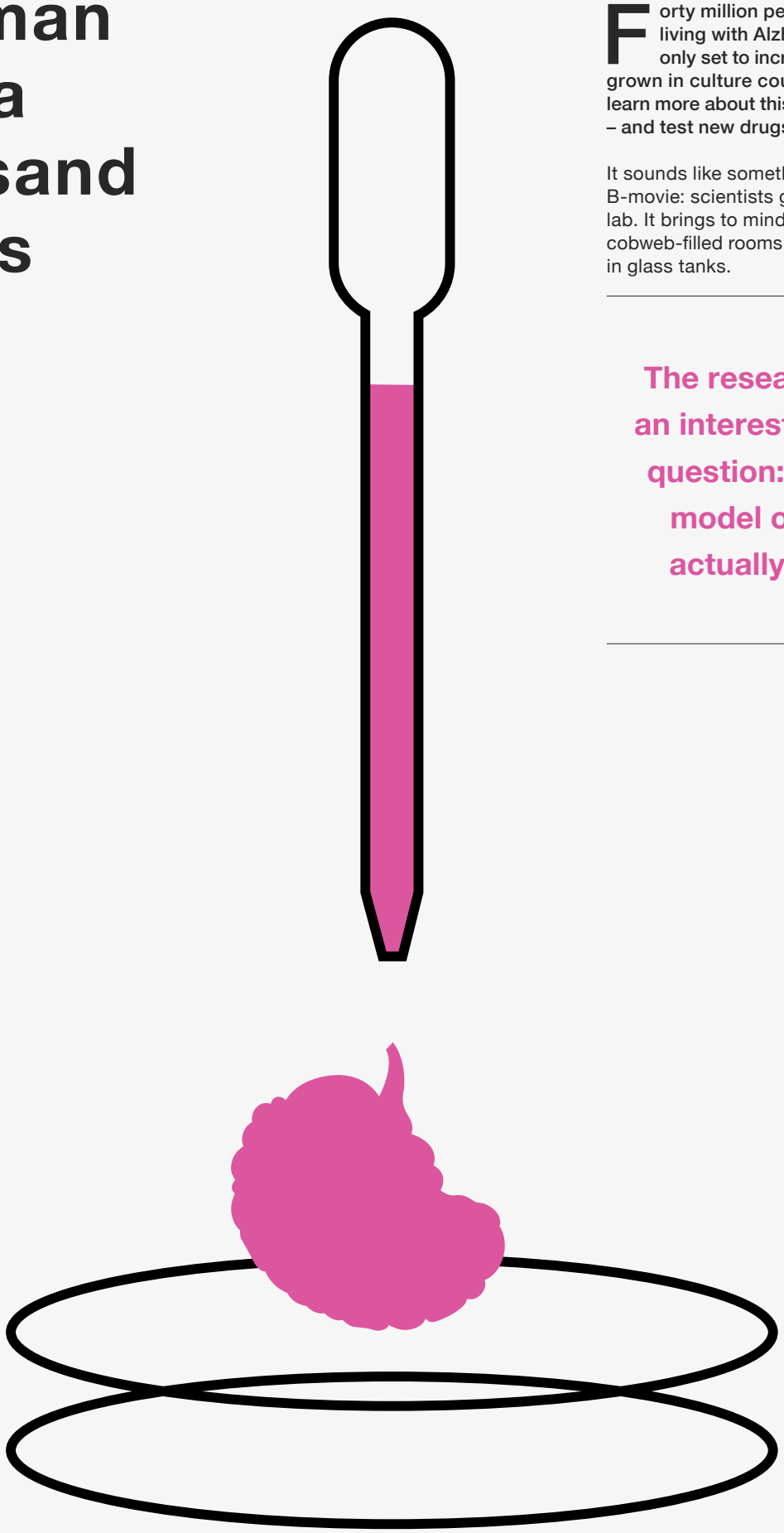
The man with a thousand brains



Forty million people worldwide are living with Alzheimer's and this is only set to increase. But tiny brains grown in culture could help scientists learn more about this mysterious disease – and test new drugs.

It sounds like something from a 1950s' B-movie: scientists growing brains in the lab. It brings to mind images of dimly lit, cobweb-filled rooms with brains pulsating in glass tanks.

The research poses an interesting ethical question: when is a model of a brain actually human?

The truth, of course, is far less gothic. The Wellcome Trust/Cancer Research UK Gurdon Institute, where the research is taking place, is light, airy and hi-tech. But although Dr Rick Livesey, who leads the study, does not like to call them 'mini-brains', that is in essence what they are: clusters of millions of nerve cells, electrically active and networked to each other, and no bigger than a freckle. What makes these 'brains' particularly useful is that they are diseased – they have Alzheimer's.

Almost 40 million people worldwide are living with Alzheimer's disease, and as more people live into old age, this number is set to rise. For a disease first described in 1906, surprisingly little is understood about its mechanisms, and there are no treatment options to prevent or reverse its progress. We do know, however, that the disease is characterised by the build-up in the brain of two types of protein: beta-amyloid, which clumps together into 'plaques', and tau, which accumulates in nerve cells to form 'tangles'. These proteins disrupt the behaviour of the nerve cells, which lose their connections and eventually die.

The standard way to study a disease is to use animals. Crudely speaking, you insert a human disease gene or series of genes into a mouse and observe the mechanisms that lead the animal to develop the disease. This approach is useful for asking specific questions, but doesn't show the disease process in a cohesive way. It can lead to the development of drugs that treat the disease in mice but fail when it comes to humans.

Instead, Livesey has turned to stem cells, building on research that won Sir John Gurdon, the man who gave his name to the institute at which Livesey now works, a Nobel Prize in 2012.

Most people who develop Alzheimer's begin showing symptoms in later life, from their sixties onwards. However, a small number of people – less than 1% of cases – have a genetic form of the disease that runs in their families, caused by a single change in one of three genes. If you carry the mutation, you will get Alzheimer's – and onset is typically in one's thirties or forties.

Livesey takes skin cells from patients with this familial form of Alzheimer's and reprogrammes them to become induced pluripotent stem cells, which resemble embryonic stem cells, with the ability to turn into almost any type of cell in the body. By guiding them to develop as neural stem cells, which create the brain's nerve cells, he makes two-dimensional clusters of nerve cells that model the cerebral cortex, the area of the brain that is affected by Alzheimer's. These clusters connect to each other, forming circuits – essential for modelling early stages of Alzheimer's, which affects the ability of neurons to communicate with each other. It's a very labour-intensive – and fraught – process that takes months. "We grow them in a sugar and salt mixture, and what do bacteria love but sugar and salt! You're always paranoid you're going to lose them," explained Livesey.

These clusters allow the researchers to replay a disease process that takes 30 or 40 years but over three or four months. In humans, our immune system does its best to fight off the disease, but eventually this clearance mechanism gets overwhelmed. "In the dish, these specialist clearance cells, called microglia, are absent so the disease process is faster. One of the beauties of our models is that we can add microglia and see what the effect of the immune system is and if we can use it to make things better or worse."

As well as allowing Livesey to study the fundamental biology of the disease, his mini-brains are powerful tools for screening potential drug candidates. To use animals for this purpose would mean using tens of thousands of mice which, as Livesey points out, "would be both impractical and ethically indefensible." Livesey puts the clusters into all 96 wells of a plate the size of a mobile phone and adds a different compound to each well. "We do this every two days for a month, monitoring to see if the disease gets better. We might try different doses of the same compound – we say well look, this is fine with whacking great amounts, but will it ever work as a real drug at concentrations suitable for humans?"

Thanks to a recent £2 million award from Alzheimer's Research UK, Livesey, together with colleagues at University College London, has also begun work on modelling more common forms of the disease. These share the same pathology as the familial forms, but may arise through fundamentally different mechanisms. "We know there is some overlap between the two forms, but there's a risk that we develop a treatment for familial Alzheimer's which won't work in the general population if the disease doesn't start in the same way."

The research does, however, pose an interesting ethical question: when is a model of a brain actually human? Livesey's models are made up of human cells and have many of the properties of real brains, but they cannot learn, do not think and are not sentient – they are not 'human' in that sense. "All of the nerve cells we make are excitatory – they're like 'on' switches. Real brains also have a second, inhibitory nerve cell type, which acts like an 'off' switch and modulates the neural circuits. These add an extra layer of complexity which is missing in our models.

These clusters allow the researchers to replay a disease process that takes 30 or 40 years but over 3 or 4 months

"But honestly, we simply don't understand the cellular basis for sentience, let alone consciousness, so we probably wouldn't know it if we saw it. Nor are we clear whether it's a scale or a complexity issue. Our neural clusters are tiny, only around a million nerve cells, whereas a real brain has about 86 billion. If we made it big enough, say a kilogram, would it become a human brain? Probably not, as we're not capturing all the complexity of the system. So what if the brain model was smaller, but captured all the complexity, like a mouse brain – would that cause ethical concerns? It's a question we cannot ignore as we move forward. But we're still a long way off there yet."

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Stem Cell Physical

"You're not going to perform lots of chemistry on it in order to decide which is the best one: you're going to pick it up and squeeze it"

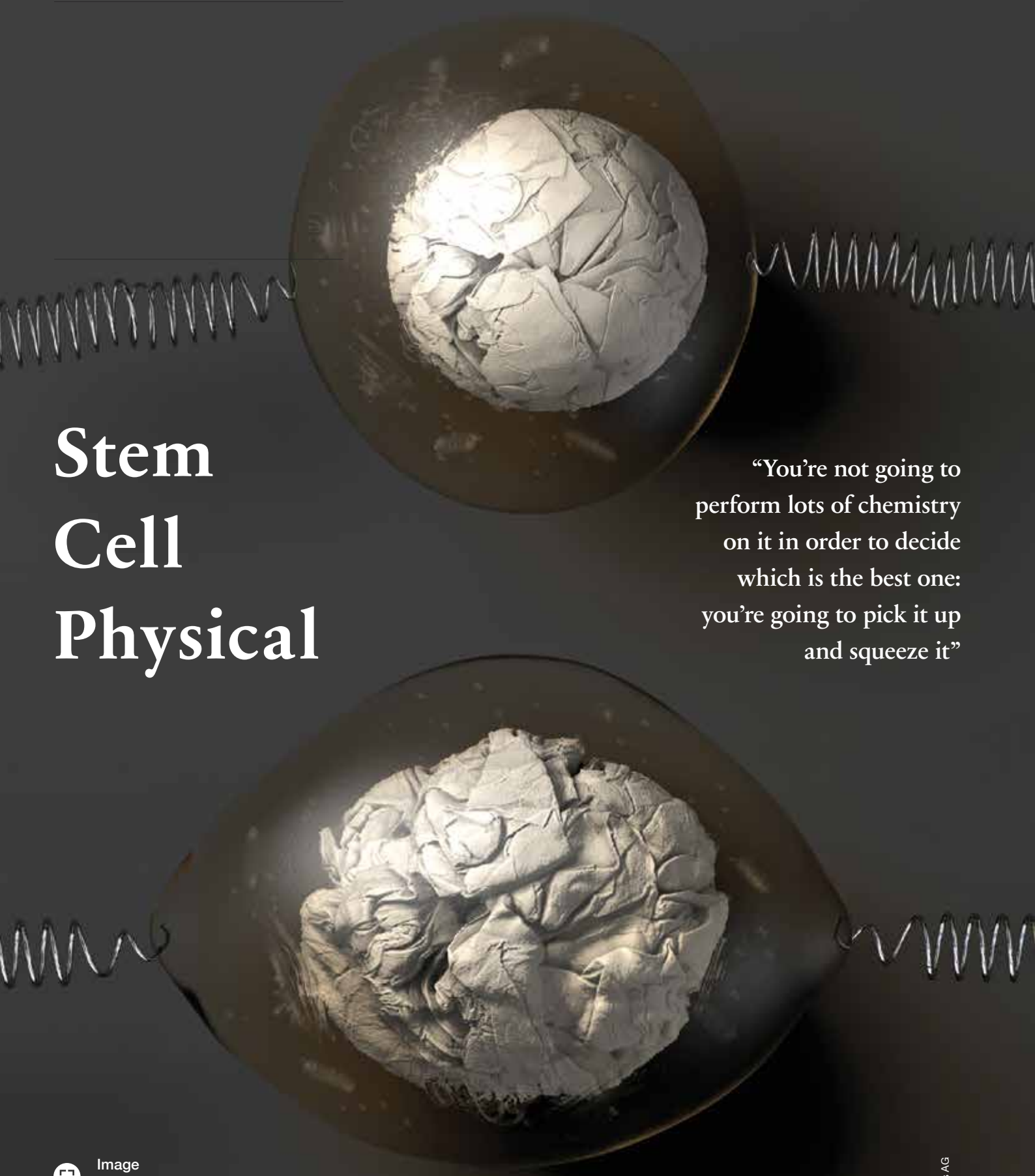

Image
Stem cells have a peculiar physical property called auxeticity: the nucleus expands, rather than thins, when it's stretched

Credit: Effigos AG

Looking at stem cells through physicists' eyes is challenging some of our basic assumptions about the body's master cells.

One of the many mysteries surrounding stem cells is how the constantly regenerating cells in adults, such as those in skin, are able to achieve the delicate balance between self-renewal and differentiation – in other words, both maintaining their numbers and producing cells that are more specialised to replace those that are used up or damaged.

"What all of us want to understand is how stem cells decide to make and maintain a body plan," said Dr Kevin Chalut, a Cambridge physicist who moved his lab to the University's Wellcome Trust-MRC Cambridge Stem Cell Institute two years ago. "How do they decide whether they're going to differentiate or stay a stem cell in order to replenish tissue? We have discovered a lot about stem cells, but at this point nobody can tell you exactly how they maintain that balance."

To unravel this mystery, both Chalut and another physicist, Professor Ben Simons, are bringing a fresh perspective to the biologists' work. Looking at problems through the lens of a physicist helps them untangle many of the complex datasets associated with stem cell research. It also, they say, makes them unafraid to ask questions that some biologists might consider 'heretical', such as whether a few simple rules describe stem cells. "As physicists, we're very used to the idea that complex systems have emergent behaviour that may be described by simple rules," explained Simons.

What they have discovered is challenging some of the basic assumptions we have about stem cells.

One of those assumptions is that once a stem cell has been 'fated' for differentiation, there's no going back. "In fact, it appears that stem cells are much more adaptable than previously thought," said Simons.

By using fluorescent markers and live imaging to track a stem cell's progression, Simons' group has found that they can move backwards and forwards between states biased towards renewal and differentiation, depending on their physical position in the their host environment, known as the stem cell niche.

For example, some have argued that mammals, from elephants to mice, require just a few hundred blood stem cells to maintain sufficient levels of blood in the body. "Which sounds crazy," said Simons. "But if the self-renewal potential of cells may vary reversibly, the number of cells that retain stem cell potential may be much higher. Just because a certain cell may have a low chance of self-renewal today doesn't mean that it will still be low tomorrow or next week!"

Chalut's group is also looking at the way in which stem cells interact with their environment, specifically at the role that their physical and mechanical properties might play in how they make their fate decisions. It's a little-studied area, but one that could play a key role in understanding how stem cells work.

"If you go to the grocery store to buy an avocado, you're not going to perform lots of chemistry on it in order to decide which is the best one: you're going to pick it up and squeeze it," said Chalut. "In essence, this is what we're trying to do with stem cells."

Chalut's team is looking at the exact point where pluripotency – the ability to generate any other cell type in the body – arises in the embryo, and determining what role physical or mechanical signals play in generating this 'ultimate' stem cell state.

Using fluid pressure to squeeze the stem cells through a channel, as well as miniature cantilevers to push down on the cells, the researchers were able to observe and measure the mechanical properties of these master cells.

What they found is that the nuclei of embryonic stem cells display a bizarre and highly unusual property known as auxeticity. Most materials will contract when stretched. If you pull on an elastic band, the elastic will get thinner. If you squeeze a tennis ball, its circumference will get larger. However, auxetic materials react differently – squeeze them and they contract, stretch them and they expand.

"The nucleus of an embryonic stem cell is an auxetic sponge – it can open up and soak up material when it's pulled on and expel all that material when it's compressed," said Chalut. "But once the cells have differentiated, this property goes away."

Auxeticity arises precisely at the point in a stem cell's development that it needs to start differentiating, so it's possible that the property exists so that the nucleus is able to allow entrance and space to the molecules required for differentiation.

"There's a lot of discussion about what exactly it means to be pluripotent, and how pluripotency is regulated," said Chalut. "Many different factors play a role, but we believe one of those factors may be a mechanical signal. This may also be the case in the developing embryo."

By bringing together physics and biology, Simons and Chalut believe not only that some of the defining questions in embryonic and adult stem cell biology can be addressed, but also that new insights can be found into mechanisms of dysregulation in disease, cancer and ageing.

Stem cells are much more adaptable than previously thought

"One of the reasons that this bringing together of disciplines sometimes doesn't work so well is that physicists don't want to understand the biology and biologists don't want to understand the physics," said Chalut. "In a sense, biologists don't know the physical questions to ask, and physicists don't know the biological questions to ask. As a physicist, the main reason I wanted to move my lab to the Stem Cell Institute is I thought there was no point working in biology if I didn't understand which questions to ask."

"There's a real effort being made to combine biology and physics much more than they have been in the past," added Simons. "It takes a bit of a leap of faith to believe physics will enrich the field of biology, but I think it's a very reasonable leap of faith. Scientific history is full of fields that have been enriched by people coming in and looking at an issue from different directions."

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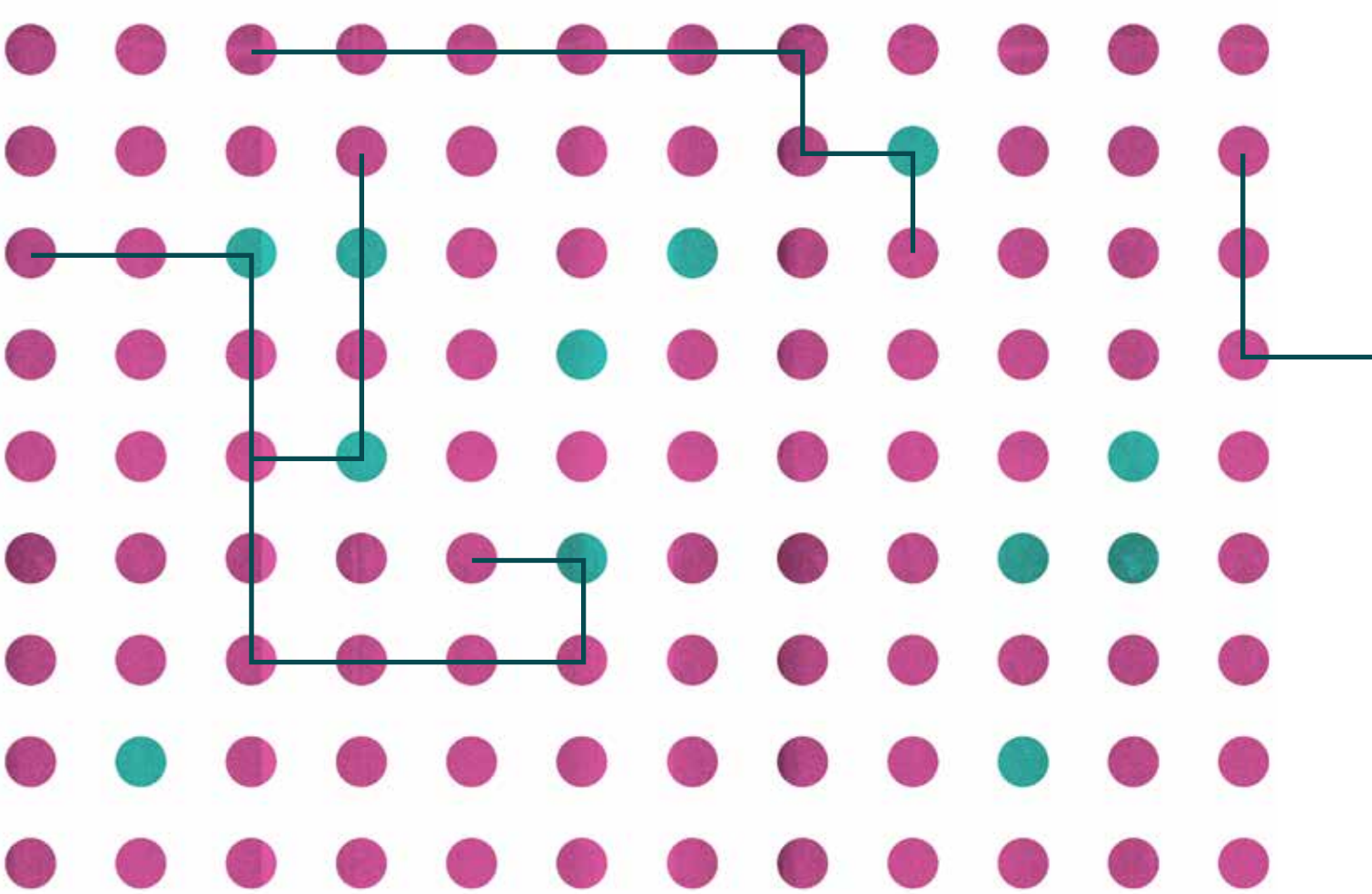


Testing time for stem cells

DefiniGEN is one of the first commercial opportunities to arise from Cambridge's expertise in stem cell research. Here, we look at some of the fundamental research that enables it to supply liver and pancreatic cells for drug screening.

Much has been written about the promise of stem cells for modern medicine, and cell-based therapies to treat diseases are now being developed by commercial companies in Europe and across the world. But it is their use both to screen medicinal drugs for toxicity and to identify potential new therapies which is increasingly being viewed as one that could have an immediate and far-reaching impact.

Cambridge-based company DefiniGEN supplies the pharmaceutical industry with liver and pancreatic cells that have been reprogrammed from human skin cells. These cells, known as induced pluripotent stem (IPS) cells, are used to test potential new drugs, and can also be used as *in vitro* models for disease.

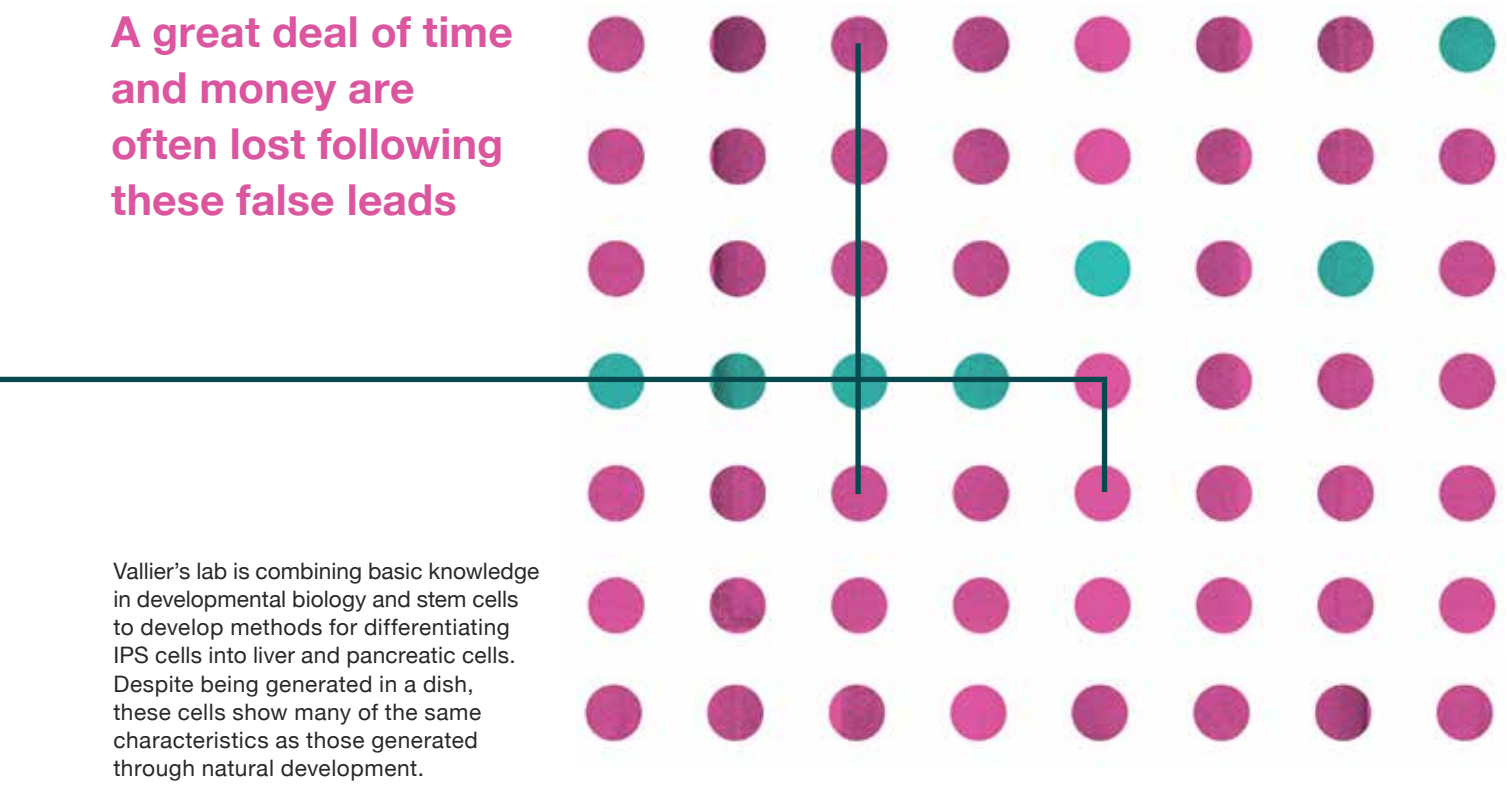
The company spun out of the University in 2012 and is one of the first commercial opportunities to arise from Cambridge's expertise in stem cell research. Its portfolio of products is based on the research of Dr Ludovic Vallier, Professor Roger Pedersen, Dr Tamir Rashid, Dr Nick Hannan and Dr Candy Cho at the Anne McLaren Laboratory for Regenerative Medicine (LRM) in Cambridge.

"Drug failure in the late phase of clinical development is a major challenge to finding new therapeutics which are urgently needed by a broad number of patients with major health-care problems such as diabetes," said Vallier. "A great deal of time and money are often lost following these false leads, and this limits the capacity of pharmaceutical companies to explore novel therapies. So, identifying toxic drugs as early as possible is vital to the efficiency and safety of the drug discovery process."

"Because we use human cells, our lab has a specific philosophy that all the data we generate is used not only for fundamental research, but also relates back to the clinic," added Vallier, who holds a joint appointment at the LRM and the Wellcome Trust Sanger Institute, and is also Chief Scientific Officer at DefiniGEN. "We are interested in how stem cells work but we also always ask how the research we're doing might have a clinical or translational interest."

IPS cells can be grown outside the body indefinitely, but can also develop into almost any other cell type, providing the opportunity to have a ready source of human cells for testing new drugs.

A great deal of time and money are often lost following these false leads



Vallier's lab is combining basic knowledge in developmental biology and stem cells to develop methods for differentiating IPS cells into liver and pancreatic cells. Despite being generated in a dish, these cells show many of the same characteristics as those generated through natural development.

In particular, the group uses a mix of IPS cells and human embryonic stem (ES) cells to understand the molecular mechanisms that could govern the onset of various metabolic diseases such as those that affect the liver and pancreas.

The liver is a large and complex organ and plays a number of important roles in the body, including digestion and the secretion and production of proteins. It is also the key organ for metabolising drugs and removing toxic substances from the body. For this reason, demonstrating that a drug candidate is not toxic to the liver is a crucial stage in the development of new drugs. It is also a test that most new drug candidates fail – increasing the cost and decreasing the efficiency of the drug development process.

A lack of high-quality human liver cells, or primary hepatocytes, means that inferior models are often used for testing potential new drugs. The cells generated in Vallier's lab, however, show many of the same functional characteristics as primary hepatocytes, both for toxicology testing and as models of liver disease, including the most commonly inherited metabolic conditions such as familial hypercholesterolaemia and alpha 1-antitrypsin disorder.

Vallier's team is also able to use these cells to model a diverse range of inherited liver diseases, offering the potential to accelerate the development of new therapies for these conditions. "There is no cure for end-stage liver disease apart from transplantation," said Vallier. "Due to an acute shortage of donors, many research groups have been looking at alternative means of treating liver failure, including stem-cell-based therapy."

Understanding the basic mechanisms behind the genesis and development of liver disease is helping his team develop new ways to generate functional liver cells that could be used to treat these conditions in future.

The researchers are taking a similar approach to the pancreas, with a particular focus on diabetes. According to Diabetes UK, 3.2 million people in the UK have been diagnosed with diabetes, and an estimated 630,000 people have the condition, but don't know it.

A promising therapy to treat type 1 diabetes is transplanting the insulin-producing islet cells of the pancreas, but there are only enough donated islets to treat fewer than 1% of diabetic patients who might benefit from this form of treatment.

Vallier's group is working to generate large numbers of pancreatic islet cells from stem cells, which could be used for transplantation-based therapy. In addition, they are building *in vitro* models to study the molecular mechanisms that control pancreatic specification in the embryo. Vallier's group has identified several genes that could be important for pancreatic development and in determining an individual's resistance to diabetes.

"Using IPS cells, we're trying to understand how individual genetics can influence development, insulin production capacity and disease onset," said Vallier. "Essentially, human IPS cells can be used to model human genetics in a dish, which hasn't been possible until now.

"Thanks to IPS cells, we're now able to discover things that are not possible to do using animal models or any *in vitro* system. Not only will this help us understand more about the mechanisms behind human development, such as how cells in the human embryo develop into organs, but it will also help with drug screening and with making more-precise drugs, which is what's really needed for the liver and pancreas. These types of *in vitro* applications are possible now, while cell-based treatments are more in the longer term. But you have to walk before you can run."

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Taking a shot at Parkinson's

Just one shot of dopamine cells derived from stem cells could be enough to reverse many of the features of Parkinson's disease for decades – and the barriers to developing such a treatment are finally being overcome.

Professor Roger Barker has a dream: by the time he retires in 15 years, he would like to see stem cell transplants for Parkinson's disease available on the NHS.

Fifteen years may seem like plenty of time to realise this dream, but there are so many contingencies that even he admits this may be optimistic. "It assumes that all our clinical trials go smoothly, that industry takes up the technology – and that 'stem cell tourism' doesn't set us back," he said.

It's not difficult to understand why people resort to stem cell tourism – going abroad, usually to countries such as India and China, to receive private, unregulated stem cell therapies (however experimental) to treat incurable conditions such as Parkinson's or multiple sclerosis. There has been much hype surrounding stem cells and, with nothing to lose, isn't it worth at least trying one of these treatments? The trouble is that they are based on very limited – if any – evidence and have the potential "to go pear-shaped", said Barker. This could damage public – and, more importantly, regulators' – confidence in the field and lead to inappropriate restrictions on legitimate research.

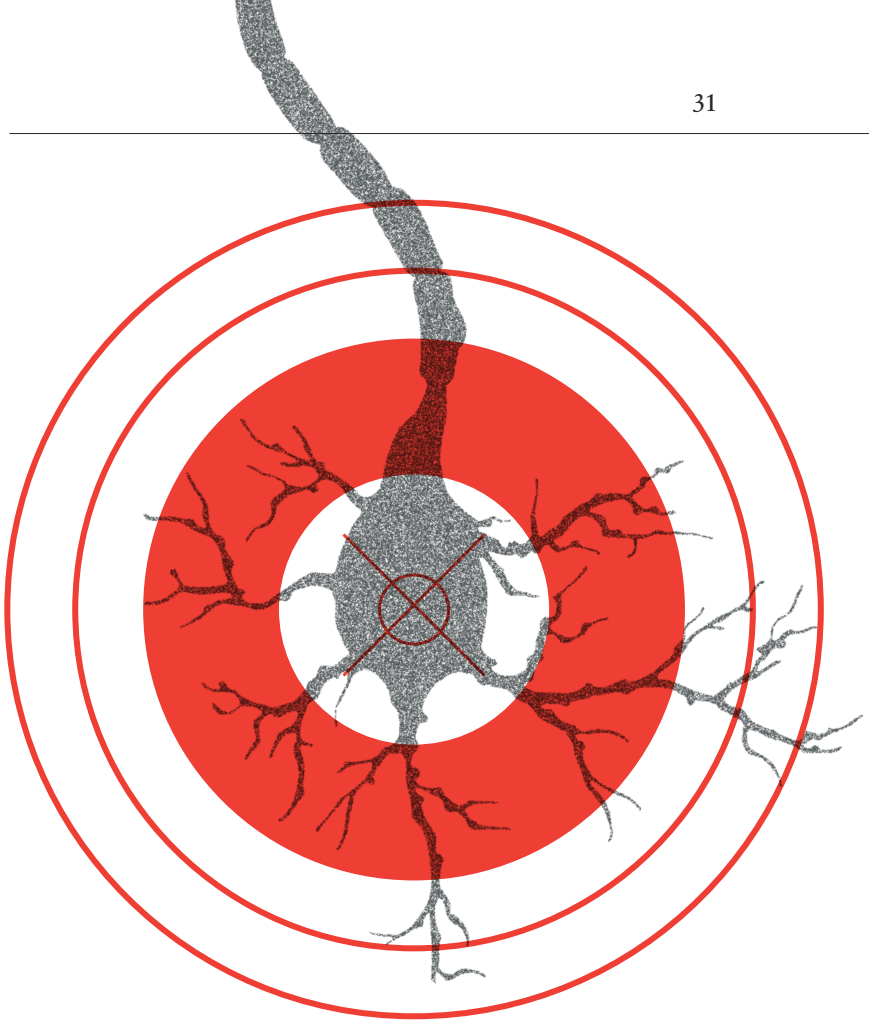
The idea of cell transplants to treat Parkinson's is not new. One of the key characteristics of the disease, which affects around one in 800 people by the time they are elderly, is the death of dopamine-producing cells in the brain. Finding a way to replace these cells could, in theory, lead to dramatic improvements in the patient's health.

An adult typically has around half a million dopamine cells in the substantia nigra on each side of the brain. When half of these cells have died, the patient will begin showing symptoms, which include a resting tremor, slowness of movement and rigidity. "One of the reasons Parkinson's disease is so attractive for cell therapies," explained Barker, "is that it is a tractable problem. If we can get just 100,000 proper nigral dopamine cells in there, it should make a difference."

Ever since the 1980s, scientists have been trialling ways of replacing dopamine cells with cells taken from aborted fetuses – a practice which, aside from ethical concerns, is not practical on a scale needed to treat the hundreds of thousands of patients in the UK alone.

The trials had mixed success. In some,

Cell therapies are relatively straight-forward to administer, through a small hole in the skull, and just one shot should last decades



patients continued to see improvements over 15 years; however, in others, the treatment not only failed, but patients suffered side effects. In part, this was due to an inconsistency in protocols, for example the age of participants, the clinical techniques used for cell delivery and the number of cells transplanted.

Now, with funding from the European Union, Barker and collaborators in Europe have developed a protocol that is more likely to provide safe, consistent and clinically effective benefits for patients. He is leading a trial in Europe to use fetal cells to treat patients, with the aim of "putting cell therapies for Parkinson's disease back on the map."

If the trial is successful, by 2018 the researchers hope to begin trialling the use of dopamine cells derived from embryonic stem cells through a new collaboration with teams across Europe, the USA and Japan. (The collaborators in Japan hope to conduct a similar trial using induced pluripotent stem cells – the patients' own skin cells, reprogrammed to become stem cells.)

The beauty of using stem cells is that they can be programmed to become almost any type of cell within the body. The risk, of course, is that they become the wrong kind of cell or 'run away with themselves' to become cancerous. Earlier this year in Lisbon, an experimental stem cell treatment – part of an approved trial to cure paralysis – reportedly led to a paraplegic woman growing a nasal tumour on her back. However, Barker is confident that new protocols have all but eliminated safety concerns – though this risk may be very real in cases of stem cell tourism.

It has still been a challenge to programme the stem cells to become nigral dopamine cells. "You take stem cells and programme them to become 'neural precursor cells'. These cells make brain; some will turn into dopamine cells and others will want to become forebrain – but if you already have a forebrain, growing another one is not going to help you! Fortunately, we've found a way round this to allow us to commit the precursor cells to become the right dopamine cells without the other cells appearing after grafting."

Pre-clinical studies in mice have shown success in treating Parkinson's disease with dopamine cells derived from stem cells, but the mice are observed only over a matter of months: Parkinson's, by contrast, is a disease that progresses over decades. Indeed, postmortems of some of the people who had previously received fetal cell transplants found evidence of the disease in some of the cells in the graft as though the protein involved in Parkinson's had caused disease in the transplant. "If that's the case, then even with stem cell therapies we could start to see pathology. But even if that is true, we know it will be decades before we start to see an effect and so this should not prevent them being adopted for treating patients."

"Of course, just because we can do something doesn't necessarily mean we should," added Barker. Treatments already exist for Parkinson's disease. The drug L-dopa can replace lost dopamine and reverse symptoms – but medication needs to be taken regularly, can cause side effects and eventually becomes relatively ineffective. Deep brain stimulation – electrodes implanted into the brain – can likewise prevent tremors and reduce some of the motor features experienced by Parkinson's sufferers, but patients need to carry around battery packs under their skin. Cell therapies, on the other hand, are relatively straightforward to administer, injected through a small hole in the skull, and just one shot should last decades.

Even so, Barker is realistic about what stem cell therapies can achieve. "They are likely to be no more effective than existing treatments. We certainly won't be curing anyone." He is also aware that to produce cells on a scale large enough for widespread use, the technology will need to be picked up by industry. "And once this becomes a commercial treatment, price may become the biggest issue."

New protocols have all but eliminated safety concerns

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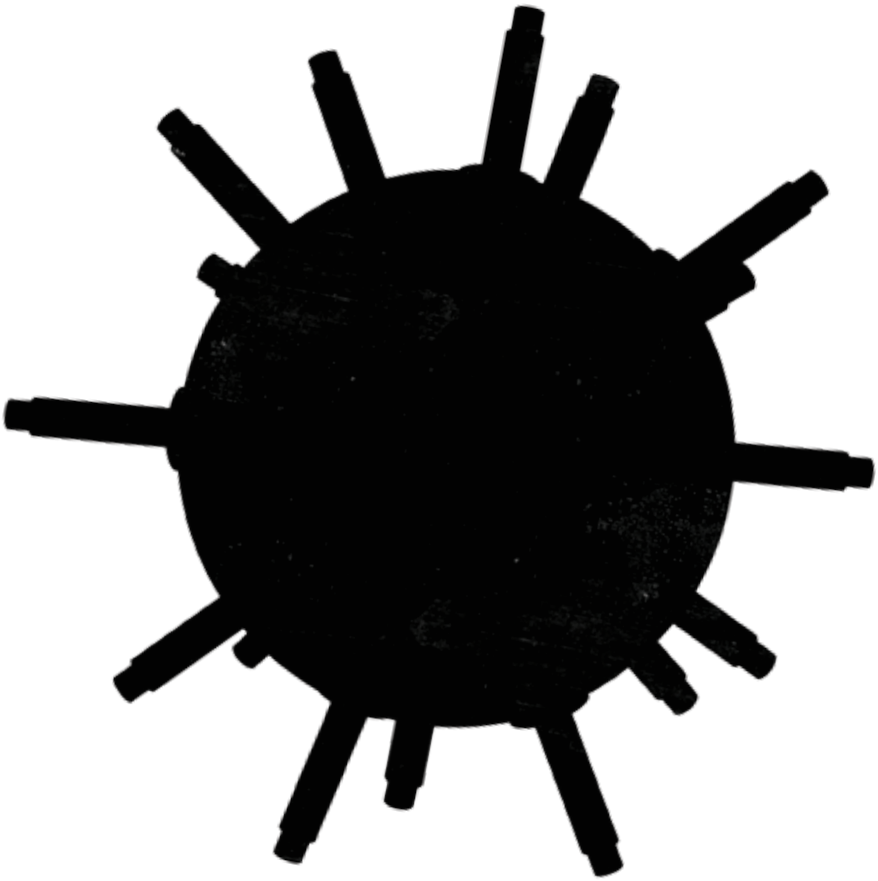
IMMORALITY AND INVENTION: the "great stem cell debate"

Human stem cell research holds promise for combating some of the most recalcitrant of diseases and for regenerating damaged bodies. It is also an ethical, legal and political minefield.

Human stem cell research is a thriving field of science worldwide – holding promise for treating diseases such as diabetes, multiple sclerosis and Parkinson's disease, as well as for furthering our understanding of how we develop from the very earliest stages of life.



But using human embryonic stem (ES) cells to improve the health of other humans has also been the subject of comment, criticism and even court cases. *Time* magazine dubbed the "complexity and drama" surrounding these cells as the "Great Debate".

Most notably, the field witnessed the 2001 restriction on funding for ES cell research in the USA by President Bush and the lifting of the ban in 2009 by President Obama. Then in 2011, the Court of Justice of the European Union (CJEU) banned the patenting of inventions derived from human eggs or their equivalent on the basis that they were human embryos, the commercial exploitation of which "would be contrary to… morality."

While religious bodies and green lobbyists use patent law to elevate the status of the embryo, scientists argue that doing so threatens research that might benefit the health of millions.

International law permits states to refuse patents where necessary to protect morality in their territory. "Yet, how does a patent examiner or a court assess whether an invention is immoral to the point that, unlike other inventions, it can't be patented? That is a particularly difficult question," said Dr Kathy Liddell from the Faculty of Law. "It is a conundrum that runs headlong into the complex intersection of law and morality, intellectual property and philosophy."

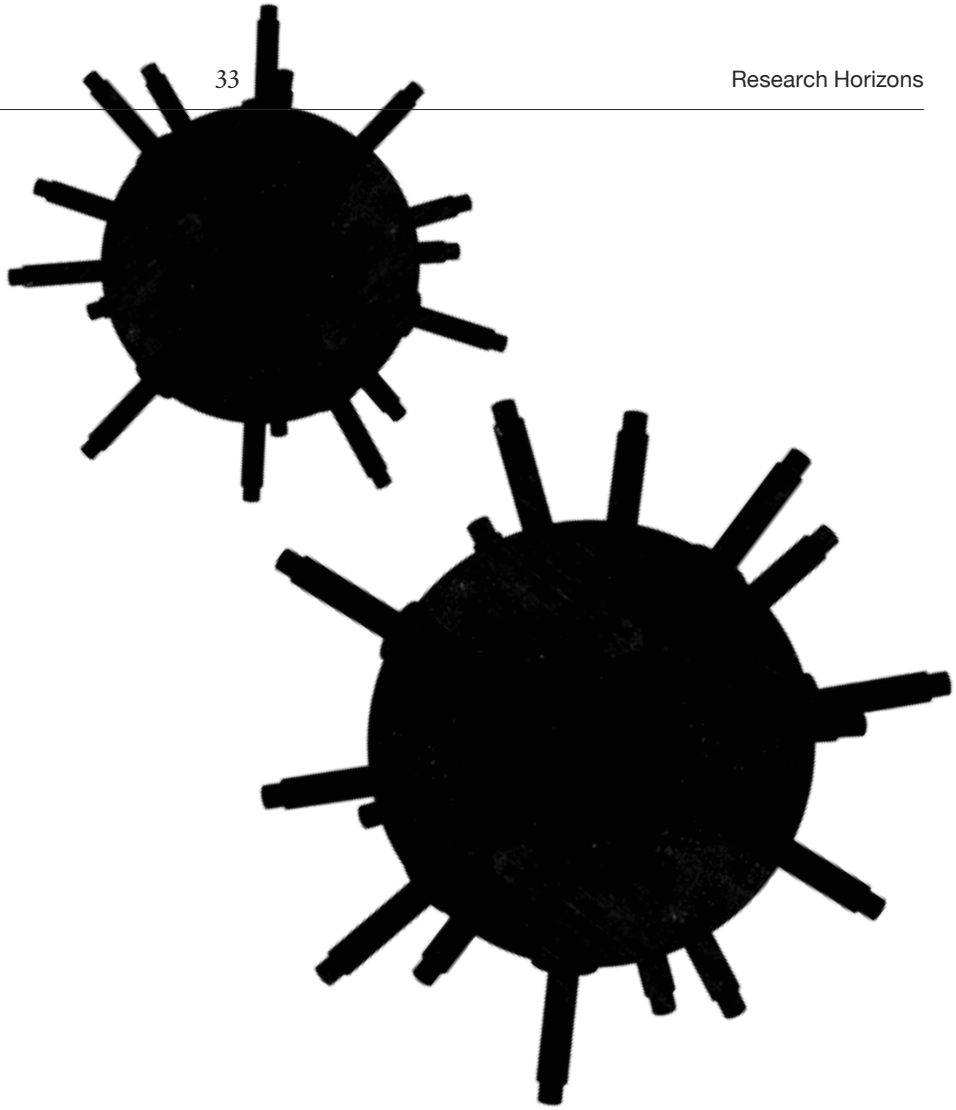
It is precisely this intersection that a new research centre in the Faculty will investigate. The new centre – funded by the Hatton Trust and the WYNG Foundation – will focus on medical law, ethics and policy relating to controversial issues such as patenting inventions involving DNA and body parts, the regulation of medical research and technologies, assisted reproduction and surrogacy, and the governance of 'big data' in the medical field, as well as the regulatory and legislative issues that stem cell research is likely to meet en route from the lab to the clinic.

"These areas need to be considered not as a *post hoc* rationalisation of events that have already happened, but alongside and ahead of technological advances," said Liddell, who is centrally involved in the new centre, as well as being Deputy Director of the Faculty's Centre for Intellectual Property and Law. "To complement the extraordinary science that is happening, we need to consider the ramifications of biomedical advances in a thorough and timely way."

Liddell's own research interests relate to the pathway that leads from the research bench to clinically effective treatments. She sees the law's role as

"We need to consider the ramifications of biomedical advances in a thorough and timely way"

Using human embryonic stem cells has been the subject of comment, criticism and even court cases



facilitating and supporting this pathway in morally responsible ways.

ES cells are useful because they are at the earliest point of human development and possess the full 'regenerative toolkit'. In other words, they can develop into any type of cell in the human body. Although stem cells found in the adult human also retain the self-renewing ability to develop into specific tissues, they cannot develop into all the tissue types needed for regenerative medicine; the genetic information needed for some developmental pathways has already been shut down.

"The CJEU was very reluctant to engage with the ethical and public policy debates surrounding human embryos. So it ended up answering the patent law questions with very little reasoning," added Liddell.

"For me, this was the biggest problem with the judgment. The Court has to have the courage, skills, wisdom and accountability to face up to the degree of judicial activism and policy shaping that is inevitable in these controversial areas. Likewise, citizens, researchers and NGOs have to accept that judges have to make difficult 'calls' in the face of moral and scientific uncertainty. They simply can't please everyone in a morally pluralist society."

Julian Hitchcock, a specialist in life science intellectual property at London law firm Lawford Davies Denoon, who advises government and the Wellcome Trust on stem cell law, agrees: "The problem I see is that the CJEU's decision sends the message that scientists engaged in stem cell research are immoral. Moreover, the CJEU's decision is being used to attempt wider assaults on research, such as in a Citizens' Initiative called 'One of Us' which suggested that the principle of human dignity applies from the point of conception. Had this initiative succeeded, not only would it have undermined research funding, but it would also have impeded the fulfilment of urgent Millennium Development Goals."

Meanwhile, the great stem cell debate continues, with a recent challenge in the High Court by the International Stem Cell Corporation over a decision by the Patent Office that unfertilised human eggs that have been stimulated to divide (turning them into so-called parthenotes) be included in the term 'human embryos'. The implication is that parthenote inventions would also fall within the CJEU's zone of unpatentable inventions. The High Court referred the issue to the CJEU and, in July this year, the Court was advised to reject part of the decision by the Advocate General.

"It's a very complex area of the law – both highly technical and highly controversial. By supporting people to develop expertise in the life sciences and the law, we can better respond to these important discussions," said Liddell.

Hitchcock added: "Formulating laws and policies that are responsive to the needs of research, and which carry the support of the public, requires a deep understanding of the ways that biology and law intersect, as well as imaginative thinking, powerful advocacy and the courage to fight an often embattled corner."

"The quintessential justification for patent protection has always been that it's important for protecting investment in research and commercialisation," said Liddell.

"We have yet to see whether the lack of patent protection for inventions involving human embryos has had a chilling effect on the transition of ideas to clinical realities, or whether it has nudged research in new, but similarly effective, directions that avoid the moral dilemmas and legal uncertainties of using embryos. We may never know – it is very difficult to gather this sort of empirical data. But for society to benefit properly and fully from medical advances, we do know that we need to be ready to enter any and all debates that wrestle with their ethical and moral implications."

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Extreme sleepover: Divining destiny in rural Armenia

Credit: Wellcome Images

Four thousand years ago, ancient Mesopotamians believed that the gods inscribed the future on sheep livers. Alex Loktionov travelled to rural Armenia to investigate what liver diviners might have seen.

The dust rises as the flock trudges through the heat haze, out of the dark ramshackle stable and into the bright Armenian sun. The temperature is soaring; it is well over 40°C, and the few stunted trees have long ceased to offer any shade. Even so, the animals move on, well aware of the huge sheepdog tracking their every movement.

They pass old bomb craters and, as the yellowish pasture opens up ahead, the herder approaches with a rope and knife. Dzhamal is very tired today: he has three herds to look after – no easy task in these conditions. He lunges at the nearest sheep. There is a brief and silent scuffle, two knots are tied and one blow is struck. Half a minute later, he suspends the dead sheep from a tree and starts dismembering because it is needed for food and fleece. Five minutes on, and I'm recording surface markings on the freshly removed liver. He looks back at me and says "we've got a good one today."

I'm an MPhil student in the Division of Archaeology, and I'm here as part of my research into decision-making processes of the Ancient Near East.

Ancient Mesopotamians believed that the gods depicted the future on the surface of a sheep's liver: its size, colour and the presence of any grooves or spots could all be interpreted as signs. I've been working on a corpus of 4,000-year-old clay tablets marked with cuneiform script detailing what omens the different liver surface patterns were thought to entail. This is my chance to see the livers for real and to compare the texts with genuine anatomy.

The sheep in Armenia are closely related to Mesopotamian varieties and have higher levels of natural parasite exposure. Although the parasites usually don't harm the sheep, they create patterns on the liver surface that were important in the fortune-telling process.

As I photograph a particularly striking parasitic lesion, I feel the content of the clay tablets come to life. It's always rewarding when a feature described in the omen corpus can be traced in genuine liver morphology, but here we have a particularly nice case. Dzhamal's comment about the sheep being a "good one" was definitely justified – although he clearly meant something altogether more gastronomic. The ancient Mesopotamians may have taken this particular set of marks as a good omen for the life of the King.

The noise of an engine sends the herd running off into the pasture, and a battered white jeep pulls up on the dirt track behind me. Three men step out – the oldest, Hakob, is the farm owner. His main focus is on selling livestock to trading partners in nearby Iran, and he's just returned from there. Full-time shepherds like Dzhamal look after his flocks. The others, Vazgen and Rafayel, are involved with Armenian television and are collecting footage for a documentary about the project. All three fought in the same regiment during the recent war against Azerbaijan and the bonds between them are strong.

As Vazgen and Rafayel go off to film the herd, I'm left alone with Hakob. The man is bursting with enthusiasm for the project and can't wait to hear what I think about his sheep's livers. We've had a range of results, with morphological alteration by parasites being very serious in some cases, and almost entirely absent in others.

Generally, the younger sheep have 'cleaner' livers as parasitic marks can accumulate with age, but it's not this simple. Liver colour and texture are also important, and these are primarily affected by the diet of the animal before slaughter.

As I tell this to Hakob, he nods vigorously and notes down the key points. Then he jokingly asks if he can feed his sheep in a particular way to get more favourable omens – Armenians are Christian, and actually have the oldest established Church in the world, but the interest in earlier cultures is still

enormous. He's raised a valid point here. I say that it's worth a try – we can't be certain that the ancient Mesopotamians knew that sheep diet affected their entrail morphology, but it's an interesting thought.

Meanwhile the men have finished their work for the day, heralded by the smell of roast lamb wafting on the warm evening breeze. As we sit by the fire and consume the tender meat, the sheepdog joins our meal. Nobody drives him away, and as the wine is poured, I notice that the dog is given some as well. I ask my friends about this, but they look surprised. As Hakob puts it, "everybody who comes to a feast should eat and drink as they wish." Why make an exception here?

And so another day draws to a close in this incredible country, where morphologically accurate sheep livers, ancient Christian rites and inebriated sheepdogs live together in harmony. And yet, as the nearby bomb craters testify, 20 years ago this land was a warzone that claimed over 30,000 lives. It's a sobering thought, and as I think of returning to Cambridge and analysing my beautiful liver photos, it just can't sink in that everyone sitting around our fire might be killed in war. My friends smile and joke in return – "the liver omens are good, so we'll be fine."

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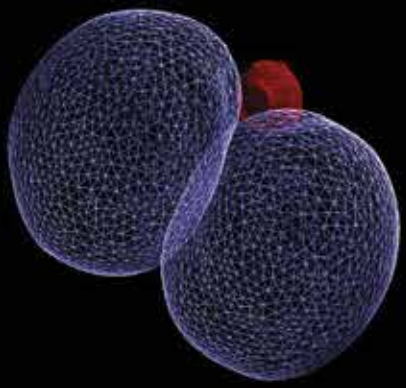
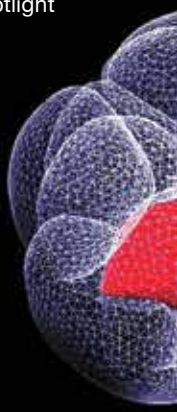
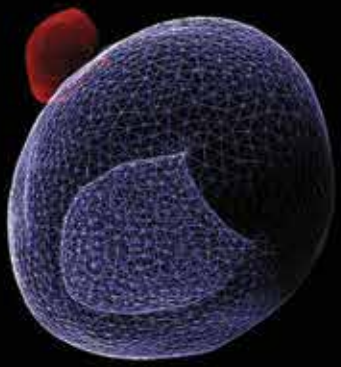
Cover
Development of the embryo (such as this mouse embryo) into an adult depends on the ability of stem cells to develop into any cell type; find out more about our research on stem cells in the Spotlight focus this issue.







Credit: Magdalena Zernicka-Goetz, Wellcome Trust/Cancer Research UK Gurdon Institute, Wellcome Images