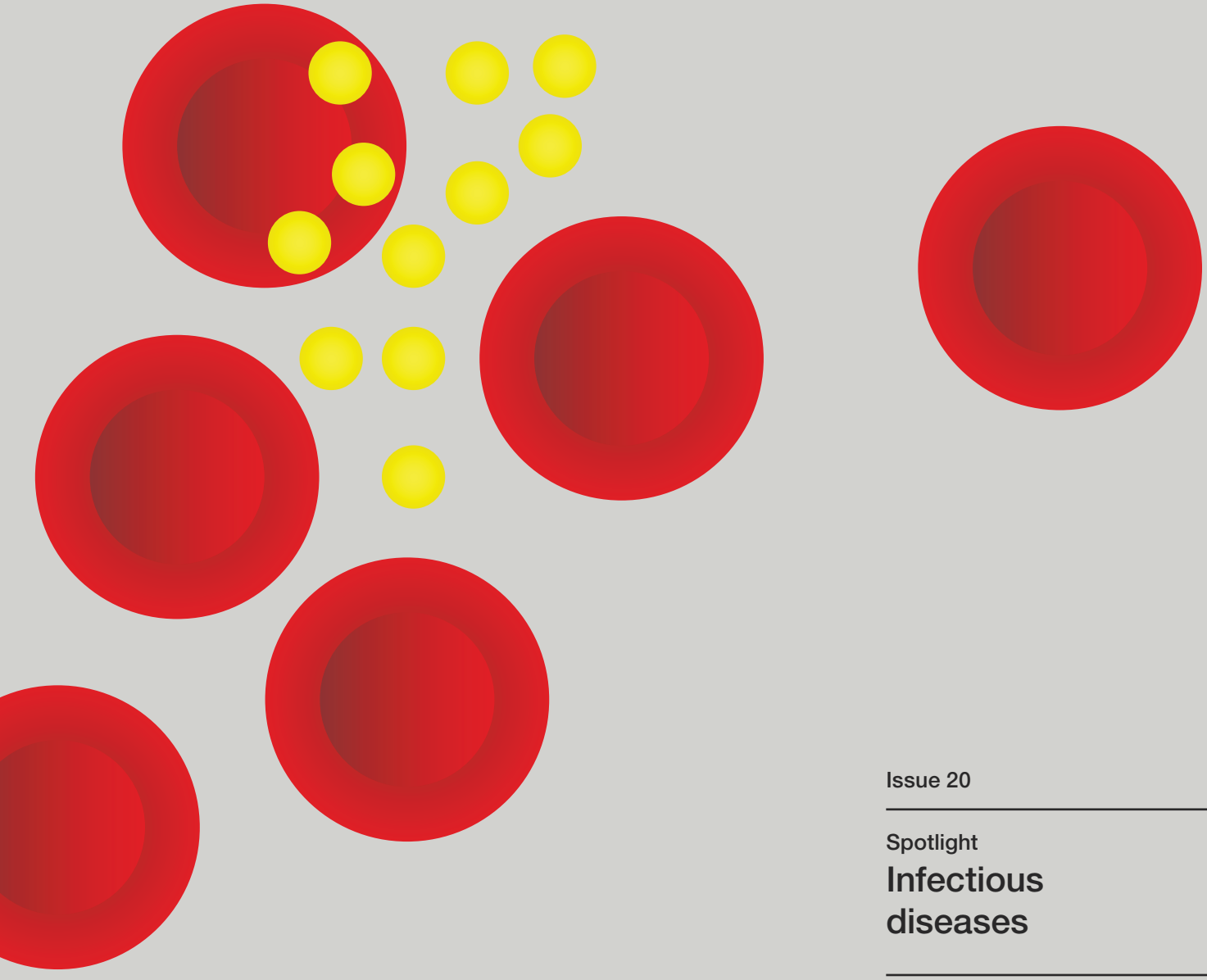
Research

Horizons

Pioneering research from the University of Cambridge



Issue 20

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UNIVERSITY OF CAMBRIDGE

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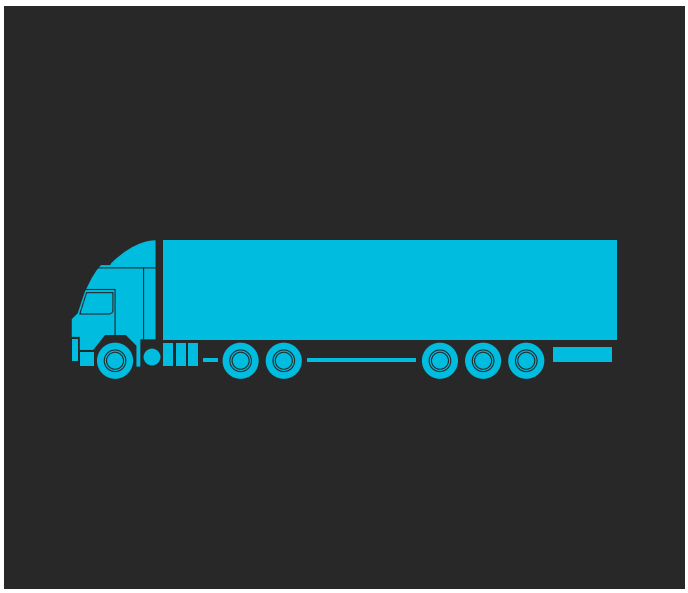

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Inside out

Welcome

Asking the right question in the right way is fundamental to academic research. It's also fundamental to market research agencies such as YouGov, whose internet-based opinion polls aim to measure the weight of public opinion. In this issue of *Research Horizons* we explore how both worlds are being brought together in a unique collaboration, combining expertise in how to ask the right question with expertise in how to interpret the responses that come back.

This collaboration is just one example of the many ways in which our researchers are working with, and drawing on the knowledge of, partners in business and industry, as well as practitioners working in the field. The Centre for Sustainable Road Freight is another. By forging close links between researchers and the freight industry, the Centre will help deliver more sustainable and efficient transport in the future.

Our spotlight focus in this issue is on the University's research into infectious diseases – a major 21st-century healthcare challenge and a Strategic Research Initiative here at Cambridge, where there is abundant cross-disciplinary expertise. Our researchers are improving understanding of the biology and history of infection, devising new therapies to combat the toll that pathogens such as HIV take on the human race, and creating tools to combat the frightening prospect of increasing bacterial resistance to antibiotics.

Elsewhere, readers will find plenty of evidence of the global emphasis of Cambridge's research. This issue profiles an exciting new project that will improve our understanding of international relations in East Asia as it becomes, once again, a major theatre in world politics. Another feature focuses on the efforts of the University's Museum of Zoology to preserve important collections for posterity and for the benefit of ongoing research.

We hope that you will find much to enjoy in this issue, the first to be published using our new design. We've thought a lot about how we want the magazine to look and feel, to reflect the innovative and life-changing research that takes place here. We hope that you like the results as much as we do.

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News

Image
New York 9/11

Conspiracy and democracy

A new project will explore the role that conspiracy theories have played in the history and culture of the past two centuries.

Conspiracy theories play a key part in the current crisis of trust that grips our societies, claim three Cambridge academics who have been awarded £1.6 million to study the history and culture of conspiracies and conspiracy theories with the aid of six postdoctoral research fellows.

The historian Sir Richard Evans has teamed up with political theorist Dr David Runciman and technology expert Professor John Naughton to run the project at the University's Centre for Research in the Arts, Social Sciences and Humanities, with five years of funding from the Leverhulme Trust.

The trio and their researchers will probe the past 200 years of conspiracy theories, asking whether the growth of democracy and free speech has changed focus from alleged conspiracies against the state to conspiracies by the state. Topics studied will range from the relationship between conspiracy theories in revolution and counter-revolution to the rise of Holocaust denial in the contemporary world.

One strand of the project will focus on the internet, and the effect it has had on conspiracy theories and mistrust of governments in particular. Comparing theories generated by the assassination of US President J.F. Kennedy in 1963 and the destruction of the Twin Towers in New York in 2001 will help understand the impact of the internet on conspiracy theories.

Has the demand for transparency in government become self-defeating? "Just how far conspiracy theories undermine trust in government will be a crucial question for this project," said Evans, and in a world of 'deep web' and Wikileaks the answers could prove revealing.

Cambridge researchers support the WHO

A newly designated Collaborating Centre will support the WHO in detecting and responding to major epidemic- and pandemic-prone diseases.

The WHO Collaborating Centre for Modelling, Evolution and Control of Emerging Infectious Diseases recognises the work of Cambridge researchers on predicting the evolution of pathogens such as influenza.

Each year, the virus infects 5–15% of the world's population and kills up to half a million people; a figure that can rise to many millions in the event of a pandemic. The WHO spearheads the annual race to develop a vaccine. As part of this process, researchers led by Director of the new Centre Professor Derek Smith in the Department of Zoology curate a global database of information on the rapidly changing variations in the influenza coat protein – the part that makes it difficult for our immune system to recognise flu from one year to the next.

The researchers provide support for WHO activities in the global surveillance of influenza and other pathogens – including rabies, foot-and-mouth disease, dengue and enterovirus – as well as recommendations on suitable vaccine strains.

"We are in the privileged position of informing public health initiatives through highly translational scientific research, using technology that allows real-time detection of circulating viruses that escape protection conferred by current vaccines," said Smith.

The Collaborating Centre draws on the wide expertise across the University in novel and emerging infections and translational science to support its core activities. It has become a University-wide multidisciplinary activity, bringing together groups in the Clinical School, Veterinary Medicine, Pathology, Architecture and Computer Laboratory.

www.whocc.infectiousdisease.cam.ac.uk

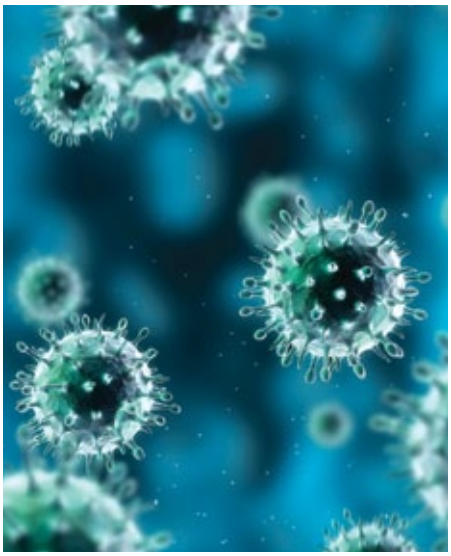


Image
Flu virus

News in brief

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

24.01.13

The Cambridge Graphene Centre is to be created with £12 million funding from EPSRC and £13 million from industry.

17.01.13

A new protocol advances solutions for more efficient teleportation - the transport of quantum information at the speed of light.

Energy Indemand

Image
Blast furnace

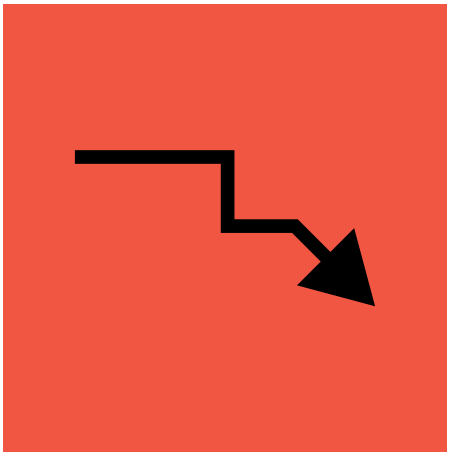
A new national research Centre led by the University of Cambridge will focus on how the UK's emissions can be lowered by reducing our demand for new materials.

The £6.2 million UK Indemand Centre will develop a better understanding of the UK's demand for energy and energy-intensive materials, to help identify opportunities to achieve a more sustainable future while supporting UK prosperity.

Created as a partnership between the Universities of Cambridge, Bath, Leeds and Nottingham Trent University, the Centre is one of five End Use Energy Demand research centres that will look into how society can save and use energy more efficiently. The centres have received £26 million funding from the EPSRC and the ESRC – together with a further £13 million from industrial partners – to support a large team of researchers over five years.

Formation of the UK Indemand Centre has come at a crucial time, as its Director Dr Julian Allwood, from the Department of Engineering, explained: "Since 1990, the UK's reported emissions have fallen by 20% but emissions caused by our consumption have actually risen by 20% over the same period: the difference is entirely due to our purchasing of goods produced by industry in other countries.

"Industrial energy is already used efficiently, largely to make materials from which we construct buildings and products. The new Centre will help to identify and pursue business, policy and technology options to reduce the UK's true emissions footprint by reducing our overall demand for new materials."



Time for an economic rethink?

With austerity measures, economic inequality and fears of financial contagion rarely out of the news, policy makers and the public wonder if economists are up to the task of understanding how the economy really works.

In the wake of these concerns, economists at the Faculty of Economics have joined forces with the New York-based Institute of New Economic Thinking (INET) to create the Cambridge–INET Institute. INET is supporting a fundamental shift in economic thinking through research funding, community building and spreading the word about the need for change, and the new Institute will join this international network of economic thinkers.

Inaugural Director of the Cambridge–INET Institute, Professor Sanjeev Goyal, said: "Our Faculty members are at the forefront of new economic thinking about individual behaviour, social and economic networks, and the transmission mechanisms which link the financial sector to the rest of the economy."

He added: "The support for the setting up of the Institute – from INET itself and from other sponsors – is recognition of the importance of this research. And it will help us in strengthening the status of the Faculty as a leading international centre for fundamental research in economics."

14.01.13
The notion of the Renaissance as a 'secular age' is to be challenged by three researchers after securing €2.3 million funding from the European Research Council.

19.11.12
Spinal cord has been regenerated in dogs with severe spinal cord injury, as shown in the first randomised controlled trial.

8.11.12
A landmark study suggests that, while physical divisions remain, divided cities such as Jerusalem and Belfast fail to thrive post-conflict.

9. 麥魔利用日本，參加美帝侵朝的罪惡戰爭。

2. 美帝自己陰力不足，陰謀重新武裝日本。


3. 麥克阿瑟釋放日本甲級戰犯重光葵，和其他戰犯。

4. 美帝慫恿日本海陸空軍，成立海上保安隊，警察後備隊，航空保安廳。

Out of the ashes of Empire

The new identities and ideologies that emerged in East Asia after the fall of Japan's Empire have rarely been studied. Now, as the region again becomes a major theatre in world politics, a new project aims to tell that history from the inside.

Barack Obama's resolution to kick off foreign policy for his second term with a tour of the Asia-Pacific region, at the end of 2012, was testimony not only to that area's growing economic importance, but also to the increasing significance of its politics. East Asia, Southeast Asia and the disputed China Seas now comprise the theatre in which the world's two superpowers meet. In the eyes of many, it is there that key decisions about supremacy, ideology – perhaps world politics as a whole – will, in future years, be made.

In the West, China's rise is the subject of constant media analysis and it has almost become de rigueur to ask ourselves how well we really understand this new giant of the world stage. But as America begins to 'pivot' eastwards, by striking deals with China's neighbours, perhaps it is as important to question how much we understand East Asia as a whole. Do we really know what drives the world view of South Korea, or Taiwan, for example? And given the growing importance of that theatre, how effective is our grasp of how these countries view one another?

Historically, the emergence (and re-emergence) of these nations after World War II is a surprisingly neglected topic. Many people are only vaguely aware that, until 1945, many parts of China, along with Taiwan, the Koreas and sections of Indochina, were at various times part of an expanding Japanese Empire that began in 1895. At its height, in 1942, this territory spanned 2.8 million square miles. Yet when two atomic bombs effectively ended the war in August 1945, the entire Empire disappeared, almost overnight.

In the wake of this collapse, new political entities appeared, but it was not always clear what the extent of their power was, or who managed which territory. "Before the Japanese Empire, nation states had not existed in East Asia the same way they had in Europe," said Dr Barak Kushner, an historian based at the Department of East Asian Studies. The next decades would see millions of lives lost as competing forces sought to stamp their authority on parts of Japan's former Imperial domain, with bitter conflicts in China, Korea, Southeast Asia, and spilling into Indochina, which later developed into the longer Vietnam War.

Post-war East Asian identities formed, then, not in the context of China's rise, but Japan's retreat. Historians, meanwhile, have tended to investigate this story from America's viewpoint, not least because they lacked access to many first-hand sources that could tell the tale from an Asian perspective. Now that is beginning to change. Recent years have witnessed the declassification of numerous government and private archives. Even China recently opened up many of its Ministry of Foreign Affairs records up to 1965. For researchers, this is a golden opportunity to examine and understand what motivated and inspired the emergent powers of East Asia as they came into being.

Kushner is the Principal Investigator for a major new project which, over five years, will attempt to research that issue. Funded by the European Research Council, its title is 'The Dissolution of the Japanese Empire and the Struggle for Legitimacy in Postwar East Asia, 1945–1965'. Its main focus, however, will be the war crimes trials that took place in East Asia after the war, as the new administrations

Images
Cartoons produced as state propaganda in China during the 1950s; such materials, together with court documents and a wealth of other archives, offer new avenues for research to aid understanding of internal relations in East Asia

Credit: Center for Research Libraries in Chicago

attempted to bring Japanese war criminals, and those people who were believed to have supported the Japanese regime, to justice.

The records of those trials offer a perhaps unrivalled view of how political and legal authority was brokered. As these countries stepped out of the Imperial shadow, the trials became statements of whom they believed themselves to be as Chinese, Korean, or Taiwanese citizens, rather than subordinates of Japan.

This was not simply a matter of enfranchising former Imperial subjects, however. Ethnicity, let alone loyalty, in East Asia was exceptionally blurred. Millions of Japan's own people remained in both Asia and the western Pacific. Their own stricken government did not want them back and many wanted to stay. In some countries, like China, where Chiang Kai-shek actively courted the Japanese to help him in the civil war, their expertise was still much in demand. Elsewhere, people who had for decades lived as Imperial subjects were, in the space of a few weeks, expected to abandon that way of life and all its symbols for something more 'indigenous'. Many, not surprisingly, struggled to understand what that meant. Identity was flexible to say the least.

Against that backdrop, the trials began. "The business of identifying who was in power and how a break with the past was to be achieved all came out in the trials," Kushner said. "They were platforms from which the new authorities could make a statement about their emergent identities. That was not an issue that the Americans, conducting trials in Japan itself, had to worry about; for them identity was a moot point."

For this reason, the project will not look at the US-backed 'Tokyo Trial' that arraigned the 'Class A' war criminals who had prosecuted Japan's war. Instead, it will focus on 5,700 class B/C criminals who were tried around East Asia. These were people who had allegedly committed crimes on the ground – rape, murder, illegal incarceration,

As these countries stepped out of the Imperial shadow, the trials became statements of whom they believed themselves to be

the abuse of POWs, or general 'crimes against humanity'. Tens of thousands more were tried for treason and collaboration. In both cases, the penalty, if found guilty, was often death.

The process varied across the region. In China, 30,000 people were charged from 1945–1947 and 15,000 convicted for treason alone. Such was the zeal of the Kuomintang that in the end evidence collection was capped because the courts could not cope, and the government was more concerned about the civil war with the Communists. In Korea, by contrast, tensions along the 38th parallel induced the southern administration to ignore collaborators altogether, and set about trying Communists from the start. In Taiwan, even identifying collaborators was coloured by the trials' function as a stage for the Chinese Nationalists as they sought legitimacy.

Kushner believes that as this process went on, over almost 20 years, 1945 became less significant as a marker for the war's end and the dawn of a new age. As well as the trials themselves, media coverage, films, literature, monuments and memorials reinforced specific views of what had happened under the Japanese as these cultural responses emerged from the judicial process. And in Japan itself, many people adopted the stance of part-chastened aggressors and part-victims of deeply partial tribunals, in what Kushner calls a "discordant swirl of public opinion." Little wonder that he anticipates the project will lead not only to a powerful retelling of this chapter in East Asian history, but "policy-relevant findings regarding Asian regionalism" as well.

One reason that ideology and identity during this period remain understudied is that many historians have, understandably, focused on the details of war crimes themselves rather than on the subsequent trials. Accounts of the latter have also tended to dwell on specific and personal aspects of the process, such as individual memoirs, or localised grudge-matches that played out during the hearings. Kushner hopes to move beyond this, arguing that while personal recollections are important in the historical record, the legal process was an expression of broader, large-scale ambitions that offer a genuinely transnational perspective on East Asia after the war. "The war crimes trials are the point at which the precedents for public attitudes thereafter are set up," he added. "They provide a written record on which a number of post-war policies about authority would be based. The time is now ripe to investigate them, and start a new historical assessment from the inside."

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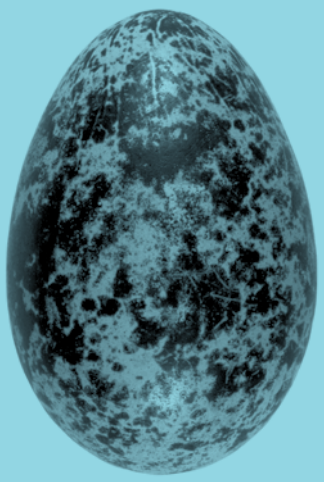


A museum for the future

Credit: Museum of Zoology and Jacqueline Garget

The University Museum of Zoology contains far more than a record of the past. Ambitious redevelopment plans will enable enhanced use of its unique collections for research into global issues from climate change to conservation.

1 million insects, 30,000 bird skins, 10,000 sets of eggs and over 3,500 fossil vertebrates: the Museum of Zoology is a treasure-trove of information about the natural world from 400 million years ago to the present day. "We have extraordinarily rich holdings," said Museum Director Professor Paul Brakefield, "from the biggest collection of dodo bones outside Mauritius, to finches collected in the Galapagos by Charles Darwin during his *Beagle* Voyage."

The Museum is on the brink of a redevelopment programme that will provide state-of-the-art facilities to benefit all users, from researchers to students to the general public. Early curators of the Museum – originally established as a showcase for collections such as those by Darwin – exhibited great foresight in creating a resource that is informing research in all areas of biology, and may have still-to-be-discovered uses in the future as new technologies are developed.

"We need to preserve and expand the collections so they continue to be used effectively across a wide range of research into the future, from understanding how life evolved, to finding ways to conserve biodiversity in a changing world," said Brakefield.

Informing ecological research

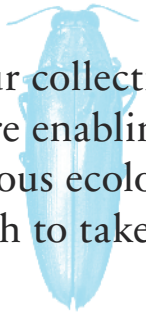
"The only way we can hope to keep track of the animal world is to identify things, and part of this is describing new species," said Dr William Foster, Curator of Insects at the Museum. "When they've been described, they have to be deposited in a designated museum such as Cambridge as a Type specimen." Cambridge's large collection of 'Type' specimens is of the highest scientific importance, providing the universal references for classifying and naming species.

Experts at the Museum such as Dr Henry Disney, who has amassed the largest collection of scuttleflies in the world, collaborate with scientists to help determine whether new finds are indeed new species. "I took Henry a specimen we collected in the rainforest in Southeast Asia and he knew straight away it was a new species, which he subsequently named *Danumphora fosteri*," said Foster.

Foster studies insect diversity in the rainforests of Southeast Asia. "We've mainly studied the beetles and ants of the canopy, and the Museum provides a solid reference collection to inform our work," he explained. "Our aims are to understand why there are so many species in the tropics compared with temperate regions, what controls this, and whether such diversity is important. To do this we have to identify everything."

Foster's research is investigating what happens to insect diversity when forests in Southeast Asia are cut down and replaced by oil palm, a high-value crop for which demand is expected to double by 2030. "Of course there's a huge reduction in diversity overall," he said, "but it's been found that some species, like bees and wasps, actually increase in diversity, while other forest specialists are replaced by 'tramp' species." "If we can add to our collections from the last few centuries," added Brakefield, "these can help to build up an accurate picture of how their distributions have changed over time, and how this may have been affected by external factors such as climate change and deforestation."

Foster aims to find a way to preserve insect diversity within the oil palm plantations themselves, without reducing yield: "If we can get more things growing on the trees, or more understorey vegetation, we could potentially increase biodiversity and enhance useful processes like pest control and leaf decomposition. Our collections are enabling this rigorous ecological research to take place. We not only need to know the number of species, but what they are, and the only way to do that is by using reference collections."



"Our collections are enabling rigorous ecological research to take place"

Evolution of terrestriality

Elsewhere in the Museum, Professor Jenny Clack, a Curator and palaeontologist, studies the evolution of early tetrapods, the four-limbed animals that evolved from fish and moved to a terrestrial environment at the end of the Devonian era around 360 million years ago. Her work relies on the Museum's fossil collection, and its ability to acquire new fossils for study following their discovery.

"We've been working on material from a crucial period in history, called Romer's Gap, from the end of the Devonian to about 340 million years ago," Clack explained. "At the start of this period something happened to cause a mass extinction, so there's a dearth of fossils from many major groups of organisms. When we pick them up again in the fossil record, the picture has changed completely. Life on land has become fully established and diverse, laying the foundation for the future evolution of the planet, including the appearance of humans. We see fully terrestrial tetrapods, whereas the ones in the Devonian were all semi-aquatic."

What happened to cause the change is unknown. "We really have very few clues as to how, and under what circumstances, tetrapods became terrestrial, walking animals." Diverse tetrapod fossils have recently been found at several sites in Scotland. With funding from the Natural Environment Research Council, Clack and colleagues are now commencing a suite of investigations at these sites and on the fossils themselves to help understand exactly what happened at the end of the Devonian, and how life re-established itself.

State-of-the-art analysis

Modern technology is increasingly being used to advance understanding of the natural world. In a paper published in June 2012 in *Nature*, Clack describes how she and colleagues made CT scans of dozens of fossil tetrapods still embedded in rock, and then used sophisticated software to digitally separate the bones from the rock, generate an image of the whole skeleton, and manipulate this to determine the range of movement of each joint. "We found that early tetrapods couldn't do a walking step, which indicates that limbs evolved before the ability to walk," said Clack. "There's a lot of material in the Museum stores still in the original rock it was found in – there are almost certainly things waiting to be discovered here that could tell us something new about evolution."

Brakefield is keen to use cutting-edge genome sequencing techniques on ancient DNA extracted from the bones, feathers or soft tissue of some of the Museum's exceptionally preserved specimens of animals that are now extinct. "By combining our resources with expertise at the Sanger Institute, our aim is to produce whole genome sequences from specimens including fossil dodo bones, the giant auk and Steller's sea cow. These can provide us with a far more complete reconstruction of how extinct organisms fit into the tree of life, and give new insights into the genetic changes underlying evolution."

To fully realise the potential of its priceless collection, the University is raising funds to completely refurbish the Museum, in conjunction with plans to create a new International Biodiversity Conservation Campus for the Cambridge Conservation Initiative. The recent award of a Heritage Lottery Fund development grant for the Museum marks a major step towards providing an exciting modern environment for lifelong learning, teaching, research and the preservation of the collections. New conservation-standard stores and a rare-book archive will be created, with space for new acquisitions across the entire collection.

"We want to conserve and preserve what we have, and also gain the potential to add to our collections, to keep them relevant for future research," said Brakefield. "The refurbished Museum will have a fantastic new research space where people can use the collections even more effectively."

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HOW TO ASK THE QUESTION

A unique partnership is marrying the latest public opinion with a spectrum of major research into national and global political issues.

Public opinion is a crucial element of our democracies, but it's not an easy thing to gauge. Cutting through the bluster of an hysterical media to get to the beliefs, concerns and opinions that people actually hold dear takes skill and resources. YouGov, the international online opinion research agency, are polling specialists who gather opinion data. They are experts in asking the right questions.

But, without in-depth knowledge of the area being polled – and YouGov polls across a huge range of areas – the answers that come back can end up adding to the noise of empty headlines. The experts in asking questions always need more experts in the things they ask the questions about.

It struck both Dr Joel Faulkner Rogers (Academic Director at YouGov) and Stephan Shakespeare (YouGov CEO), that there was potential for a "natural marriage" between YouGov and Rogers' old University – he was a postgrad in International Relations at Cambridge. They approached Professor Andrew Gamble, then Head of the Department of Politics and International Studies (POLIS), with a mutually beneficial offer. The result was YouGov–Cambridge, born in 2011.

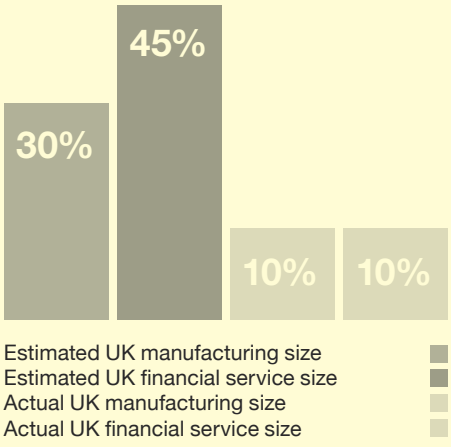
"YouGov has powerful resources for measuring what people are thinking and doing around the world," said Rogers, "and tapping into the research expertise at Cambridge to support some of our polling enables opinion research that really gets under the skin of global trends and events. YouGov has always valued its academic links, so the partnership enables us to provide an amount of pro bono polling to support University research and teaching".

As YouGov grows internationally – linking with offices in the USA, Europe, the Middle East and China – the wider global context is imperative and the latest research from Cambridge experts in numerous fields can help create polling surveys that probe complex and hard-to-reach issues. These data also feed into academic work at the University, providing researchers with unique access to YouGov's opinion data-gathering.

"For example, YouGov produced a survey in the run-up to the 2011 Egyptian Parliamentary Elections with Dr Anne Alexander, an expert in Middle Eastern politics at Cambridge. For YouGov, Dr Alexander's input was invaluable in understanding a fast-changing national and regional environment. Meanwhile, Dr Alexander gained access to our expertise and technology – getting survey data from around 2,000 Egyptian respondents in a short space of time," highlighted Rogers.

A key aim for the YouGov–Cambridge project is getting tomorrow's graduates engaged directly with public opinion research. Tom Barker, a postgrad student in POLIS researching the political economy of work, utilised the YouGov–Cambridge project with the help of Rogers to devise a survey investigating British attitudes to key issues for the UK economy.

GDP



The surprising results showed that people vastly overestimate the size of the UK's manufacturing and financial service industries, believed to be 30% and 45% of GDP respectively, when in fact each are only around 10%. Barker and his colleague Umberto Marengo wrote this research up with Rogers as a short paper for the Institute for Public Policy Research, providing excellent experience for the early career researchers.

"YouGov–Cambridge is a fantastic

venture which encourages us as researchers to look outwards – to better understand popular attitudes towards political issues," said Barker. "I recently gave a presentation to encourage fellow junior researchers to take advantage of this partnership, highlighting the benefits it could bring to their own work.

"Having received such great support, I'm keen to devise a new poll related more directly to my PhD topic to form part of the empirical component of my thesis."

The Wilberforce Society, Cambridge's student-run think-tank, is also engaged with the YouGov collaboration on programmes of student research and events, and Rogers is working closely with Cambridge Public Policy and the new Master's in Public Policy (MPP), looking at ways its students will be able to get involved.

"Opinion trends are vital to any area of public policy in the modern information age. YouGov will help to provide the public opinion element of the MPP, sourcing case studies to support the curriculum, along with work placements and teaching contributions," Rogers explained.

But, while POLIS remains on home turf, YouGov–Cambridge already stretches far beyond, with collaborations including the Judge Business School and the Department of Land Economy, in particular its Cambridge Centre for Climate Change Mitigation Research, which is running the Cambridge Retrofit project – a key study for YouGov–Cambridge.

The retrofit project looks at best practices for increasing sustainability in existing buildings, working initially in Cambridge city itself. YouGov–Cambridge is producing several surveys to support the project – exploring tenants' attitudes towards energy efficiency in rented properties, followed by landlords' attitudes – to build a set of "actionable data" to help guide the research. "The YouGov–Cambridge polling is central to our work. While we can design incentives for retrofits and calculate the impact on UK carbon emissions, it is difficult to engage the property community in carrying out the necessary retrofits," said Professor Douglas Crawford-Brown, who is heading up Cambridge Retrofit.

"The polling gives us access to a national sample of attitudes, providing an evidence base for how best to interact with the public on these issues, and for rolling it out nationally. We will then collaborate on polling of international attitudes towards combined energy, economy and environment policies aimed at reducing risks of climate change and driving the decisions of global thought leaders."

The online polling methods used by YouGov are increasingly recognised at the University for having powerful advantages, according to Rogers, including the quality and scope of samples. Surveys are usually completed by a carefully selected panel of adults in the given country. Information is recorded, and added to over time, providing both longitudinal and demographic depth of understanding about attitudes and behaviour.

Online polling allows researchers to reach large numbers of people in a short period of time, and often encourages greater honesty from respondents on sensitive subjects, through surveys that offer complete privacy and anonymity.

For Rogers, these are exciting times, with ever-more polling projects in the pipeline at Cambridge. As well as current work, new studies will include a joint effort with the Centre for Science and Policy involving the attitudes of British scientists to government policy, and work with Land Economy on climate change and energy bills. Among the new POLIS projects is simultaneous polling across the USA, UK and China to research public perceptions of economic confidence.

In addition, YouGov-Cambridge now holds an annual conference at the University involving students, researchers and senior academics, plus thought leaders from government, business and media – where specially conducted international surveys are discussed live by experts. "It's a great, physical way to combine polling and academic expertise with people from the field, all in one room," said Rogers.

"My hope is that this collaboration can assist with connecting the University's world-leading research – from academics and students alike – with what's happening in public opinion and policy making at a national and global level, so that Cambridge thinking is as relevant as it is heavyweight."

www.yougov.polis.cam.ac.uk

AND WHAT TO DO WITH THE ANSWER

Keep on trucking

Whether it's a bag of oranges or a tank full of petrol, the commodities we rely on will have come down the motorway in a fleet of lorries crisscrossing the country to keep supermarket shelves full and fuel reservoirs topped up. Now a new Centre will look at how road freight can be made more sustainable.

Almost everything we consume arrives on a truck, even if its road trip represents just part of its overall journey. Lorries bring us the things that we need – but, as substantial users of diesel, they do so at significant cost. That cost is not just financial; it's also social and environmental.

A new initiative – the Centre for Sustainable Road Freight – was launched in December 2012 to look at the 'big picture' of the movement of freight by road in the UK and to explore ways of making the sector more economically, socially and environmentally sustainable. The reduction of carbon dioxide and other greenhouse gas emissions, which contribute to global warming, is a key objective of the programme, in tune with the government's targets of 34% reduction (compared with 1990 levels) by the year 2020, and 80% reduction by 2050.

The Centre, which has £5.8 million funding for the first five years, is a partnership between the University of Cambridge's Department of Engineering and Heriot-Watt University's Logistics Research Centre. It is headed by Cambridge's Professor David Cebon, an engineer with expertise in the dynamics of heavy vehicles, who leads a team of ten academics from the two institutions: "The Centre draws on the strengths of both institutions – Cambridge's skill set in engineering and Heriot-Watt's capabilities in logistics. It brings together experts from a wide range of fields, from the aerodynamics of vehicles through to logistical operations and driver behaviour."

A vital feature of the Centre is its close links with the freight industry. Of the initial funding, £4.4 million will come from the Engineering and Physical Sciences Research Council and £1.4 million from a new industrial consortium. The consortium will comprise freight operators such as DHL, John Lewis Partnership, Tesco and Wincanton, as well as vehicle industry partners including Firestone, Goodyear, Haldex and Volvo. These companies will help to set the research agenda and set the pace in the adoption of results. With fuel representing, on average, 45% of operating costs, and with aggressive emission-reduction targets set by government, the road freight industry has substantial incentives to minimise its use of diesel.

The programme will look at the most influential factors that govern fuel usage by the road freight industry to develop a road map for the industry and help it meet emissions reduction targets. The key is to have a sequence of practical interventions, both logistical and engineering, which are socially acceptable and economically attractive, and which drive down emissions. "It is no use having an ambitious end point if there is no practical way to get there," said Cebon. "Our aim is to focus on the big-picture issues and make sure that the most important factors get the right amount of industrial and political attention, at the right time."

To illustrate this point, Cebon explained how an improvement in vehicle aerodynamics would reduce fuel consumption for motorway operations – but that advance in performance may be small when matched against other factors such as traffic congestion, which is heavy on fuel consumption. He said: "A viable reduction in fuel consumption due to improved vehicle aerodynamics is 5%. If you set this against the extra fuel used in one unscheduled vehicle stop, it would take about

400,000 trucks

45 km of continuous driving by the improved vehicle to break even. Although improved aerodynamics does make a difference, traffic flow is hugely influential, meaning that improved road systems, better route planning and delivery time scheduling can make a big contribution to reducing fuel consumption."

The Centre is guided by the 'triple bottom line' approach to sustainability: planet, people and profit. In devising workable solutions, the second and third of these are as important as the first. The public might complain about emissions and noise, and lobby to keep trucks out of residential areas, but lorries are the lifeblood of the country's economy. Without freight transportation by road, the economy would grind to a halt within four or five days. All along the supply chain, companies rely on just-in-time delivery systems working 24 hours a day, seven days a week, on narrow profit margins. According to the latest figures, some 400,000 lorries and 290,000 drivers deliver around 3.9 million tonnes of freight on a daily basis.

One of the aspects of freight transport that offers most potential for reducing fuel costs, and thereby emissions, is to maximise loads. When a vehicle delivers its freight and returns empty, the energy used for the return trip serves no useful freight purpose and the fuel consumption per freight task is increased by 70%. The solution to this problem lies in improved logistics management and collaboration between different operators. Similarly, when freight is taken off a large articulated truck and put on two smaller trucks, 40% more fuel is used. In this case, there is an opportunity for the development of large vehicles that are more manoeuvrable in narrow streets and safer for vulnerable road users such as pedestrians and cyclists.

Modern trucks are designed to be aerodynamic with smooth shapes that offer least wind resistance and skirts to streamline air flow. An area of aerodynamics that has thus far been largely neglected is the underside of trucks. This aspect of truck design is being investigated by a team led by Cambridge's Professor Holger Babinsky, who has worked extensively on the aerodynamics of Formula 1 cars.

Measuring the flow between the underside of a truck and the ground it is passing over presents a particular challenge because of the difficulties in running realistic wind-tunnel tests. Using a model truck, researchers have developed a method of scaling up some of the parameters by towing the model through water in a glass tank. "We think that the underside of a truck contributes as much as 30% of total drag and that by redesigning the underside we can reduce that figure by 10 to 20%," said Babinsky.

Over the next five years the Centre's research programme will generate a series of software and hardware systems. Software systems will include logistical management and vehicle routing tools, software to advise operators on energy efficiency options, and databases of logistical information. These will help operators with the complex task of planning deliveries to meet the needs of suppliers and consumers while minimising environmental and social impact. Hardware systems will include improved aerodynamic systems, low rolling-resistance tyres, lightweight trailer designs and regenerative braking technology whereby the energy expended in braking is captured and reused.

"What's exciting about the Centre is the fact that it brings together so many leaders in their fields," added Cebon. "By working together and focusing on both the logistical issues and vehicle engineering we can devise solutions that will make a major contribution to sustainability in the road freight industry."

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Things The world inside a Spanish globe

Images
Spanish globe, Whipple Museum

Film & feature article available online

Study of a mysterious 100-year-old interactive toy globe – perhaps the Wikipedia of its day – is painting a vivid picture of Spain's path into the modern world.

Clearly it's a globe, but lift the northern hemisphere and you enter a startling world: volcanoes erupt, a mammoth lifts its tusks, dinosaurs clash. And amid these beautiful illustrations and encyclopaedic entries, a planetarium lies ready to re-enact the revolution of the planets around the sun at the turn of a cog.

Now, research by Sebastian Falk – working with Professor Liba Taub in the Department of History and Philosophy of Science whose Whipple Museum houses the globe – has brought us closer to understanding this Spanish toy, which he has now dated to c. 1907. Remarkably, Falks' work highlights how the globe symbolises a wave of change that swept 19th-century Spain into the modern world – from increasing trade in scientific instrumentation to a move towards an education system based on interactive learning.

This was a crucial time in Spain, he explained: "The 19th century had seen civil wars and coups with numerous failed attempts at economic reform and industrialisation. A vociferous press argued that Spain's problems resulted from inadequacies in the education system."

As a result, Spanish educational practices began moving away from passive learning towards flexible, small-group education with children learning from tactile experiences and experimentation – for which the globe, whose design is based on mass-produced central European models, would have been perfect.

For Falk, a fascination of the project has been the chance to see at first-hand how the study of 'things' – the times and places that objects were made and used, played with and discarded – can tell us about ourselves and the society around us: "Just in this one object we can see the intersection between the popularisation of science, printing technology, education, international trade and Spanish political developments."

The Whipple Museum holds an internationally important collection of scientific instruments and models, dating from the Middle Ages to the present.

www.hps.cam.ac.uk/whipple

Credit: Whipple Museum and Jacqueline Garget

Fingerprint of a killer

Can whole genome sequencing provide the forensic information needed to map and control the global spread of antibiotic-resistant bacteria?

A lethal combination of factors threatens the future of global health – the inexorable emergence and spread of pathogenic drug-resistant bacteria, and a slowdown in the development of new antibiotic drugs that are effective against these superbugs. The era of the ready and rapid cure of common bacterial infections may be coming to an end, heralding a return to a time when such diseases were the most common cause of death.

Why are bacteria so successful in fighting back? Many bacteria can divide as fast as every 20 minutes under ideal conditions, which allows them to adapt very rapidly to adverse environments. By acquiring pieces of DNA from other bacteria, strains are selected that have a fitness advantage and over time can build up a catalogue of genes that help them to survive. Acquiring DNA that codes for antibiotic resistance is a prime example of this process, and is fuelled by antibiotic use.

Halting the current emergence of ever-more resistant bacterial pathogens requires attention to the root cause, which means rigorous control of antibiotic use. This is difficult to achieve on a global scale and has had little success in much of the developing world where antibiotics are available over the counter. In the meantime, control efforts rely on tracking the emergence and spread of multidrug-resistant strains, and the rapid detection and containment of outbreaks. Researchers at the University of Cambridge believe that this is where technologies based on whole genome sequencing (WGS) could really make a difference.

Outbreaks of infection caused by multidrug-resistant bacteria create notable problems in hospitals where antibiotic use is high and patients are prone to hospital-

acquired infections, but detecting these outbreaks quickly so that they can be efficiently controlled has proved challenging.

A team of researchers from the Department of Medicine, the Wellcome Trust Sanger Institute and Cambridge University Hospitals has been using advanced WGS technologies to sequence the genomes of a range of multidrug-resistant bacteria associated with hospital outbreaks, to find out whether this approach could be used to confirm rapidly and accurately that an outbreak is taking place.

In a study published in June 2012 on the superbug methicillin-resistant *Staphylococcus aureus* (MRSA), WGS was combined with the search for tiny variations in the sequence of different strains. This showed that 'genetic fingerprints' could be used to distinguish between bacteria isolated from patients who were involved in an outbreak and bacteria isolated from those who were not. A second study subsequently showed that WGS could be used to detect the spread of MRSA from hospitals into the community, and was used to identify a carrier in the hospital, helping to bring the outbreak to a close. Efforts are now under way to apply this technology to other bacteria, including multidrug-resistant Gram-negative bacilli, a group that comprises some of the most pathogenic disease-causing bacteria.

How does this approach differ from what we can already do? "Current bacterial typing methods often lack sufficient discrimination to be able to distinguish between strains of the same bacterial species isolated from different people. This means that we cannot confirm whether transmission has taken place and so typing is not used as part of routine infection control," explained Professor Sharon Peacock, who led the recent MRSA studies. "WGS promises to inform and enhance infection control decisions. Sequencing can now be done in less than a day, which means that information is produced in time to influence clinical practice."

Peacock's latest studies have started to look at drug resistance in *Mycobacterium tuberculosis*. An estimated 650,000 cases of multidrug-resistant tuberculosis (TB) occurred worldwide in 2010, of which 9% were classified as extensively drug-resistant (XDR). It can take weeks or months to determine the full antibiotic-susceptibility profile of *M. tuberculosis* using traditional culture-based techniques, yet effective treatment of XDR TB is essential; the wrong treatment is bad news for the patient and also means that the organism can spread to, and infect, other people. Preliminary studies by Peacock's group have started to explore how fast and accurate sequencing can be at predicting the resistance pattern of *M. tuberculosis.*

Sequencing technologies are becoming faster and cheaper, but there are barriers to adopting these into routine clinical microbiology. "Generating the sequence data is within the capabilities of hospital diagnostic laboratories and can be done using easy-to-use DNA isolation and preparation kits, and bench-top sequencing machines," said Peacock, who is also a clinical specialist at the Health Protection Agency. "However, what is currently lacking is automated sequence interpretation tools that turn a string of genetic data into information that is useful to healthcare and public health workers. Analysis, interpretation and management of the data to provide a mechanism for local, national and global surveillance are significant challenges that we and others are beginning to address.

'Genetic fingerprints' could be used to distinguish between bacteria isolated from patients who were involved in an outbreak from those who were not.

"We also need to understand the cost versus benefit associated with the introduction of this technology into the NHS. Under what circumstances does the extra information provided by sequencing make a difference to patient outcome, disease control or healthcare cost, and when is it not worth doing?"

Nevertheless, she predicts that WGS will lead to a major paradigm shift in public health microbiology: "It's not a question of if, but when, this change will happen."

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Cambridge Infectious Diseases Initiative

Sharon Peacock leads a Strategic Research Initiative that is harnessing expertise in infectious diseases across the University. Here she explains how it's gearing up to play a major role in global health research, training and capacity building.

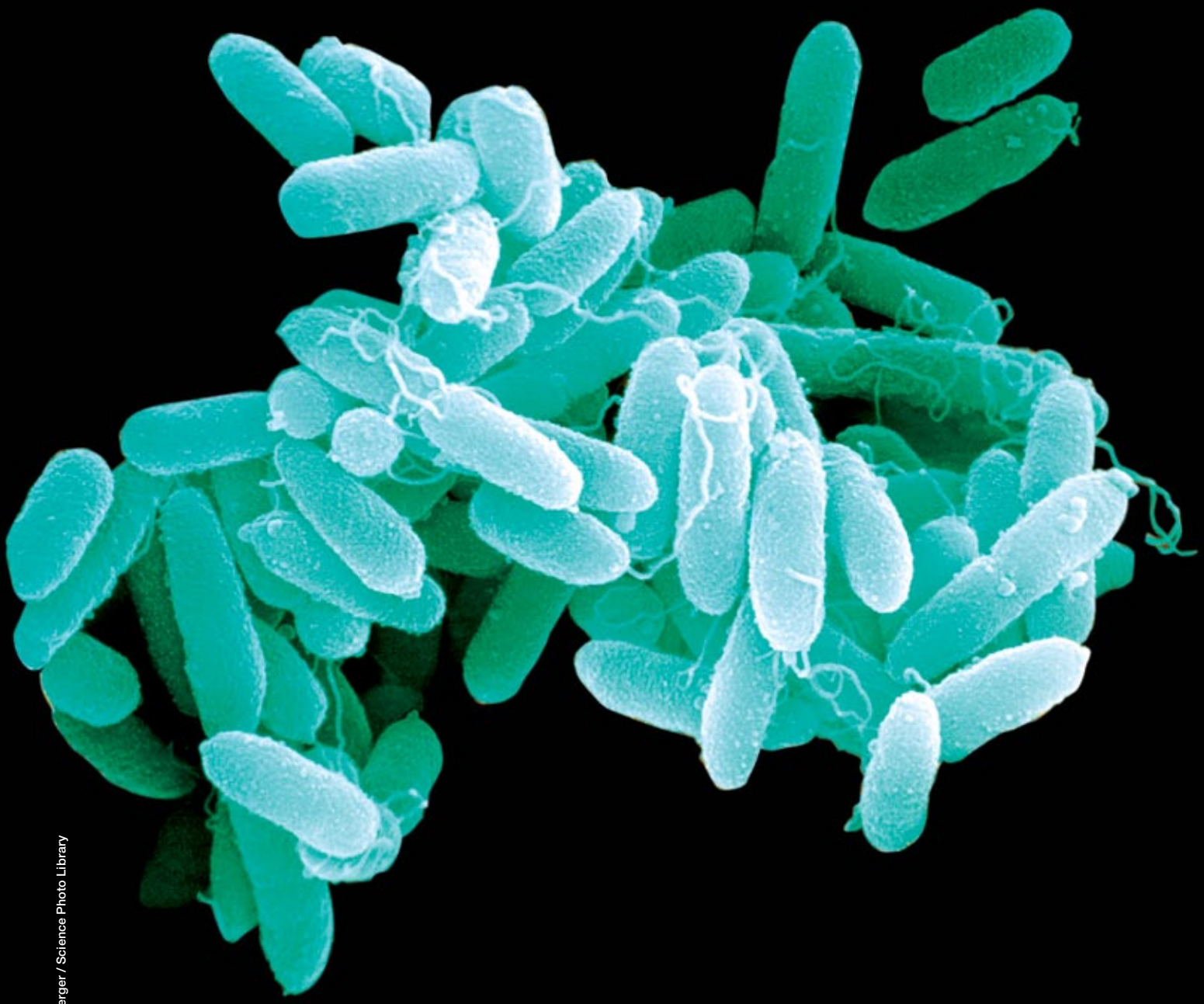
Combating infectious diseases remains as important as ever. A combination of basic and applied research has led to some extraordinary success stories, such as the eradication of smallpox. Yet history tells us that the emergence of a new infectious disease that goes on to threaten the health of the global population is a likely scenario.

The research being undertaken at the University demonstrates that infectious disease research represents a priority area in Cambridge. As highlighted in this issue of *Research Horizons*, our strengths are broad and range from fundamental biological research through to the development of new drugs, as well as understanding the history of infectious diseases.

One of the challenges faced by any university is to define mechanisms whereby research efforts can be coordinated to achieve synergies between different departments and areas of expertise. This approach is being driven in part by the growing trend for major funding organisations to develop funding calls that require interdisciplinary teams of investigators to address 'big problems', and infectious diseases research funding is no exception. The Cambridge Infectious Diseases Initiative can help to meet this need, by promoting and facilitating all forms of infectious disease research together with training and capacity building.

Over the past two years, the Initiative has played a key role in the development of a successful bid to become a Wellcome Trust Centre for Global Health Research, and in the newly designated WHO Collaborating Centre for Modelling, Evolution and Control of Emerging Infectious Diseases. It also supports a range of existing initiatives, including the THRiVE programme and Cambridge in Africa, which provide training and mentorship to African scientists – many of whom work in regions where infectious diseases take their highest toll. Cambridge Infectious Diseases promotes networking through its annual one-day infectious diseases meeting, and engagement and outreach activities are also part of its remit.

www.infectiousdisease.cam.ac.uk



Credit: Juergen Berger / Science Photo Library

Image
Pseudomonas aeruginosa work together to colonise lung tissue

Bacterial banter

A target for therapeutics

Targeting the 'conversations' that bacteria have with one another could herald a new generation of therapeutics that curb the virulence of infectious microbes.

Bacteria don't work alone. Like a well-organised gang, they wait until they are strong in number before unleashing their virulent weapons. They sense when their community has reached 'quorum' – the minimum number that must be present to transact their business – and they do so by 'talking' to each other. It is this remarkable communicative aspect of bacterial behaviour that researchers are now targeting as a way of combating infection.

Communication helps single-celled bacteria band together as a multicellular community to attack, or to defend themselves, or to respond to a change in their environment. "It's a cute trick," said Cambridge biochemist Professor George Salmond who, almost 25 years ago, was one of the first researchers to demonstrate how bacteria 'team build'. "For virulence, for instance, it's far better to attack the host with tissue-degrading toxins at the same time.

“It’s really timely to be thinking about how we can supplement the limited number of antibiotics in the pharmaceutical arsenal with new strategies”

It has maximum effect and overwhelms any immune defence system, compared with a piecemeal attack from individual cells.”

Bacteria communicate through the release of chemical signals that are picked up by their neighbours. It’s the concentration of these molecules that tells them when the gang is large enough to make it worthwhile to trigger a response. Once the concentration of the signal molecule reaches a certain threshold, it triggers population-wide changes in bacterial gene expression that kick-start cooperative behaviour.

Team building

Today, scientists know that there are many of these chemical signals – so-called quorum sensing (QS) molecules – and that they can help the bacteria carry out certain behaviours that are simply better to do as a group.

“In business terms, group effectiveness is often measured in terms of forming, storming, norming and performing, and this is effectively what bacteria do,” said Salmond. “They are almost independent at low density, but when they get to the right density they use the chemical signal to tell them to do something interesting and achieve their goal.”

Their goal might require them to perform more than one behaviour. Salmond’s work on the plant pathogen *Erwinia* – a problem in the potato industry – has shown that not only is the release of virulence factors coordinated to occur when the bacteria reach quorum but also the release of a bacterially made antibiotic. The antibiotic kills off other, non-*Erwinia,* bacteria in the vicinity.

“The virulence factors break down the potato and release nutrients that *Erwinia* can feed on, causing potato rot. But other bacteria are also present. You can imagine that if you’ve done all the work you wouldn’t want hangers-on to partake of your windfall,” he explained. “One rationale for having antibiotic production as well as virulence factor production under QS control is that you kill off your competitors to avoid them exploiting the nutritional bonus.”

Even something as straightforward as floating to the surface in a pond can be coordinated by QS, as Salmond and Professor Ray Goldstein in the Department of Applied Mathematics and Theoretical Physics are discovering in research funded by the Biotechnology and Biological Sciences Research Council (BBSRC).

Bacteria living in a watery environment often have tail-like flagella that help them swim, swarm or glide. But such movement is an energetically costly process. Salmond and Goldstein have found that some bacteria, such as *Serratia*, have an ingenious way of propelling themselves out of a crowd of different bacteria that is competing for the same nutrients and oxygen. Using QS to coordinate their activity, the bacteria produce tiny intracellular gas vesicles that float them to the pond surface, enabling them to colonise new territory as a team. “That’s the notion of bacterial gang culture – you hang together – it’s the chemical language of survival,” added Salmond.

Hijacking communication

In recent years, given its central role in coordinating virulence, QS has emerged as a promising target for therapeutic strategies aimed at treating bacterial infections. The idea is to interfere with the signalling mechanism to minimise destructive tissue damage and to increase the chance that the body’s immune system will clear the infection.

Researchers in Cambridge are concentrating their efforts on the activity of one bacterium in particular – *Pseudomonas aeruginosa* – a somewhat notorious human pathogen feared in hospitals because of its multidrug resistance and it being a lifelong burden to patients with cystic fibrosis (CF). In CF patients, the bacterium colonises the lung, forming a difficult-to-eradicate colony, or ‘biofilm’, which is frequently resistant to antibiotics. Crucially, both the production of virulence factors and the formation of biofilms are under QS control.

“With the increasing incidence of multidrug resistance in pathogenic bacteria, it’s really timely to be thinking about how we can supplement the limited number of antibiotics in the pharmaceutical arsenal with new strategies,” explained biochemist Dr Martin Welch, who collaborates with Salmond. “The idea is to develop QS inhibitors that make the bacteria avirulent and less prone to form biofilms, resulting in less lung damage and greater sensitivity to conventional antibiotics.”

Welch and Dr David Spring in the Department of Chemistry are developing approaches that disrupt QS in *P. aeruginosa*. Spring’s team of organic chemists are experts in the development and screening of small molecules that interfere with the QS process. “We have made antagonists to homoserine lactone QS molecules that block the action of the real signalling molecules, and some of these look as if they might be lead compounds for drug discovery,” said Spring.

With funding from the BBSRC, the researchers have more recently focused on a particular QS molecule named PQS, and are leading the field in the development of a ‘chemical toolbox’ for the study and modulation of this signalling mechanism.

The team is also investigating agonists – small molecules that upregulate QS – as Spring explained: “If we can activate QS at a lower density of bacteria then this could stimulate the immune system to attack when it has a chance of clearing the infection, before it is overwhelmed by a large-scale bacterial attack. What’s especially attractive about disrupting QS is that the system is not essential for bacterial survival so it’s less likely that resistance will develop quickly to a treatment targeting this process.”

However, they are quick to point out that medical applications may be many years in the future. “There is a catch for CF – it seems that the longer the bacteria live in the CF lung the more likely it is to drop QS, and perhaps antagonists may only be relevant at early stages,” said Welch. “Which is why we need to understand QS fully – when the process happens and when it doesn’t.”

Welch’s current research has focused on developing a ‘metagenomics’ approach that will enable researchers to sequence all of the many bacteria, not just *P. aeruginosa*, that reside in the CF lung. “It’s a zoo in there. All of these bacteria are probably chemically communicating to form an ecological network. We are particularly interested in understanding what impact antibiotics have on the global population structure; this may allow us to streamline future therapeutic interventions.”

What seems increasingly clear is that bacteria are far more sophisticated than single cells living in splendid isolation, as Salmond concluded: “You have to admire them. You develop a great respect for bacteria when you learn how they communicate together. They colonise every niche of the planet, were here long before we appeared and, no doubt, will be here long after we’re gone!”

I Left to right

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OFFENSIVE MANOEUVRES IN THE WAR AGAINST HIV

Anti-HIV drugs can now significantly prolong life but do not restore health – patients must take the drugs for the rest of their lives. New approaches to therapeutics may hold the answer to finding a cure.

It was in Los Angeles in 1981 that the first report emerged of an unusual cluster of patients whose immune systems appeared to have failed. This report is now acknowledged as the first scientific account of an infectious disease that was to become the HIV/AIDS global epidemic, infecting 60 million people and killing 25 million to date.

Three decades later, and with more than 20 antiretroviral drugs to combat HIV, treatment can now significantly prolong life and reduce the rate of viral transmission. For some patients, life expectancy with uninterrupted treatment is now similar to that of someone who is not infected with HIV – not the death sentence it once was – and the global rate of new infections is at last declining.

Yet, current therapies do not fully restore health and, in resource-poor settings, patients often lack access to antiretroviral drugs. Moreover, because the virus has the ability to insert its genetic material into the genetic material of the patient's cells, 'latent' viruses can re-emerge at any point, necessitating lifelong drug treatment.

"There is no imminent prospect of a vaccine, and there may not be one in the way that we have for measles and mumps, where our own immune system can clear the virus," explained Andrew Lever, Professor of Infectious Diseases in the Department of Medicine and Honorary Consultant Physician at Addenbrooke's Hospital. "The bottom line is 60 million immune systems have had a crack at eradicating HIV and all have failed."

The virus is both adaptable and versatile, escaping drug treatment by mutating the structure of its proteins. Patients require combinations of drugs – an approach known as highly active antiretroviral therapy (HAART) – because this reduces the chance that a virus will mutate sufficiently to escape all.

Continued research efforts are therefore urgently required, as Lever explained: "The big areas in HIV research are finding new drugs to complement the ones we've got already, so as to outrun the virus in terms of resistance, and finding a means to eradicate the latent virus."

Lever's research, which has been investigating the mechanisms of HIV infection for almost 25 years, is helping to tackle both of these challenges.

Structural traps

Anti-HIV drugs typically target viral proteins that are involved in the process of entering or exiting the cell. But, as Lever explained, this lies at the heart of resistance to the virus: "Proteins are very adaptable. Time and again the virus escapes the drug by altering its protein structure so that it still functions but the drug no longer recognises it. We decided instead to target the virus' RNA genetic material."

Lever's previous studies had provided fundamental insights into the way in which RNA is packaged, a process that he realised could provide a remarkable opportunity for a completely new type of antiretroviral therapeutic.

For the virus RNA to be packaged and released from the cell as an intact virus particle, it must twist itself into a three-dimensional knot-like structure. It was this structure which Lever and colleagues discovered is used as a packaging signal by the virus. To form the structure, the sequence of the RNA must be highly conserved between viruses. As a result, opportunities for 'escape mutation' are limited. A virus protein called Gag uses the knot-like structure to pick out the viral RNA from the thousands of cellular RNAs that are an integral part of the process by which a cell translates the information in its DNA into molecules that enable the cell to function.

Interfering with Gag binding can potentially stop the virus spreading from cell to cell. In collaboration with Professor Shankar Balasubramanian and Dr Neil Bell in the Department of Chemistry, and researchers at the University of Sussex, Lever is now using this phenomenon as the basis for designing novel antiviral drugs. In parallel, work with Professor David Klenerman in the Department of Chemistry is providing the first high-resolution data on the precise conformation of the RNA structure.

The goal is to create a 'structural trap' in which small-molecule drugs lock the RNA in a conformation that can no longer interact properly with Gag. Targeting the function of RNA through its 3D structure is a new direction for antiviral drug discovery, and sufficiently challenging to receive funding from the Medical Research Council Milstein Fund – specifically intended for 'high-risk, high-reward' studies.

Using an assay they developed for measuring the interaction between Gag and RNA, the team is now screening a library of small drug-like molecules for those with potential to interfere with the process. "Although it's very early stages, the molecular hypothesis that we started with for targeting this structure has taken us to a situation where we have molecules that look like they are doing something interesting in the assay," said Balasubramanian. "Being able to target RNA in this way would be a paradigm shift in terms of new therapeutics for HIV, and other infectious diseases."

Will RNA-directed therapeutics overcome viral resistance? "It's a good question and untested," added Balasubramanian. "Once we find a good small molecule that disrupts binding and packaging then we can address exactly this question."

Curing HIV

Drug discovery is a key area for the future. However, the scientists also have their eyes on an even bigger prize – a cure for HIV – and a new collaboration between five UK Biomedical Research Centres (BRCs) is now working towards understanding how to rid the body of latent virus.

"Because latent virus exists only as genetic material, essentially indistinguishable from the genetic material of the patient's cells, it's effectively hidden. The patient's immune system can't see these infected cells and the drugs can't target them," explained Lever. "The reservoir of infection sits there for years because it's in very long-lived immune cells. Even if you suppress the virus right down using drug treatment, as soon as you stop the drugs it bounces right back with viruses that, based on their genetic sequence, are historically very old, so these have been latent for a long time."

The new project, CHERUB (Collaborative HIV Eradication of Viral Reservoirs: UK BRC), funded by the National Institute for Health Research, brings together researchers from Imperial College, King's College Biobank, University of Cambridge, University College London and University of Oxford, and is the first pan-BRC cooperative project to compete internationally in a new field of biomedical research.

Lever leads the Cambridge contribution along with Dr Mark Wills and Dr Axel Fun from the Department of Medicine. "Until we learn how to eradicate the latent virus then all we can do is contain it," Lever explained. "CHERUB will work in collaboration with NHS Trusts and the pharmaceutical industry to recruit new patient cohorts for studies that range from fundamental laboratory research through to large-scale clinical trials of novel agents."

The Cambridge researchers will develop an assay to detect latent virus that will be used to provide a measure of the relative success of drugs, as well as expand current research areas to learn new ways to rouse the virus from its latency.

"All HIV patients have latent virus – it's a fact of life," added Lever. "You can suppress active viruses with current conventional drugs so that the patient's immune system recovers but you can't get rid of the latent virus. The aim now is to suppress the virus to the point where the immune system recovers but at the same time to wake up and eradicate the virus from the latently infected cells. And then we are talking about a cure."

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"The bottom line is

60

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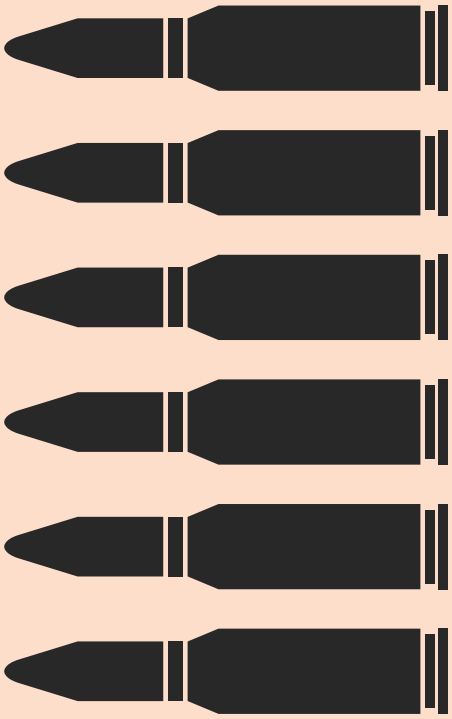


Finding malaria's weak spot

A ground-breaking imaging system to track malarial infection of blood cells in real time has been created by a collaboration catalysed by the University's Physics of Medicine Initiative.

After over a decade of research into malaria, biologists Dr Teresa Tiffert and Dr Virgilio Lew at the Department of Physiology, Development and Neuroscience found their efforts to observe a key stage of the infection cycle severely hindered by the limits of available technology. An innovative collaboration with physicist Dr Pietro Cicuta at the Cavendish Laboratory and bio-imaging specialist Professor Clemens Kaminski in the Department of Chemical Engineering and Biotechnology is now yielding new insights into this devastating disease.

Under attack

Malaria is caused by parasites transmitted to humans through the bites of infected mosquitoes. According to the *World Malaria Report 2011*, there were about 216 million cases of malaria causing an estimated 655,000 deaths in 2010. Tiffert and Lew established their malaria laboratory in Cambridge in 1999 to investigate the most deadly form of the parasite, *Plasmodium falciparum*. Becoming increasingly resistant to available drugs, this species in particular is a growing public health concern.

Their current focus is a mysterious step in the life cycle of *P. falciparum* occurring inside the infected human's bloodstream. The parasites, at this stage called merozoites, attach to and enter red blood cells (RBCs) to develop and multiply. After two days, the new merozoites are released and infect neighbouring RBCs. Over several days, this process amplifies the number of parasitised RBCs and causes severe and potentially lethal symptoms in humans.

"A huge amount of research has been devoted to understanding the RBC penetration process," said Tiffert. "The focus of many vaccine efforts is the molecules on the surfaces of both parasite and red cell that are instrumental in recognition and penetration. Our collaboration with Clemens developed new imaging approaches to investigate what happens in the cells after invasion. But the pre-invasion stage, when a merozoite first contacts a cell targeted for invasion, remained a profound mystery. Our research indicates that this stage is absolutely critical in determining the proportion of cells that will be infected in an individual."

For invasion to occur, the tip of the merozoite has to be aligned perpendicularly to the RBC membrane. Tiffert and Lew are focusing on how this alignment comes about, which has proved a formidable technical challenge. "The merozoites are only in the bloodstream for less than two minutes, where they are vulnerable to attack by the host's immune system, before entering a RBC. To investigate what is going on we need to record lots of pre-invasion and penetration sequences at high speed, using high magnification and variable focusing in three dimensions. And the real challenge is to have the microscope on the right settings and to be recording at exactly the time when an infected cell has burst and released merozoites – something that is impossible to predict," said Tiffert.

Techniques used by previous investigators have produced few useful recordings of this process occurring in culture, but from these an astonishing picture is emerging. "The contact of the merozoite with the RBC elicits vigorous shape changes in the cell, not seen in any other context," said Lew. "It seems clear that this helps the merozoite orientate itself correctly for penetration, because all movement stops as soon as this happens. The parasite is somehow getting the RBC to help it invade."

A collaborative approach

Cicuta, a University Lecturer involved in the University's Physics of Medicine Initiative – which is bringing together researchers working at the interface of physical sciences, life sciences and clinical sciences – met the trio by chance three years ago. He realised he could use his background in fundamental physics to pioneer a new approach to understanding malaria. "It's been a gradual move for me to apply what I've learnt in physics to biology," he said. "From the physics point of view, RBC membranes are a material. This material is very soft and undergoes deformations and fluctuations, and I was interested in understanding the mechanics involved during infection with malaria."

Drawing on his expertise in the development of experimental techniques, Cicuta collaborated with Tiffert, Lew and Kaminski to pioneer a completely automated imaging system that pushes the boundaries of live cell imaging, enabling individual RBCs and merozoites to be observed throughout the process of infection. The research was funded by the Biotechnology and Biological Sciences Research Council and the Engineering and Physical Sciences Research Council.

Film available online

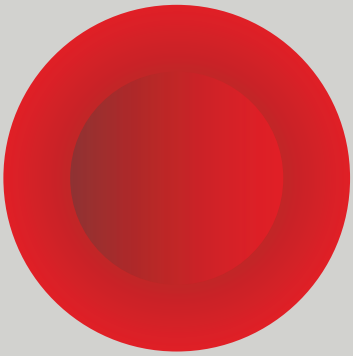
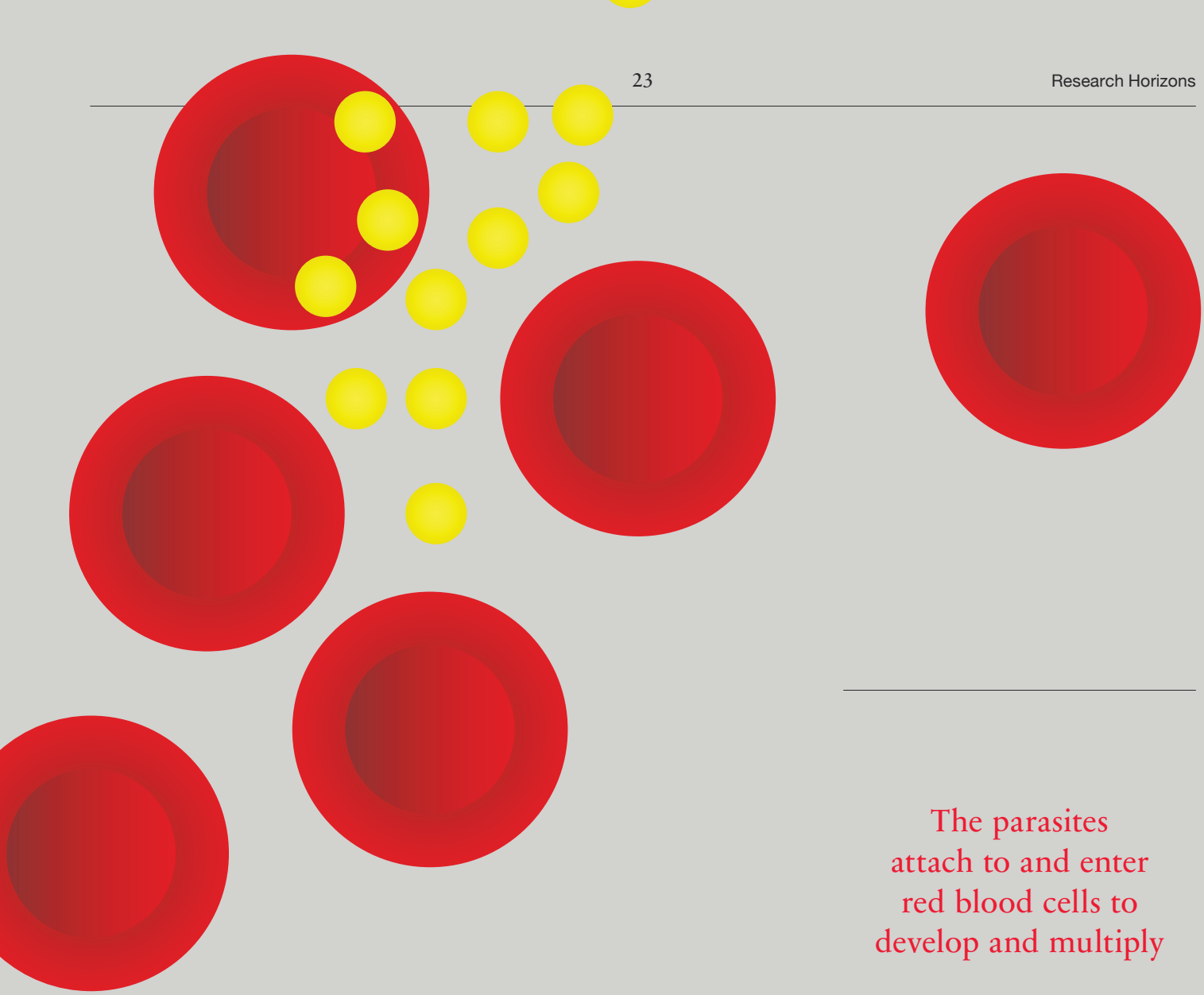


Image
A new imaging system is enabling individual red blood cells to be observed throughout the process of infection by malaria parasites

"This microscope can not only run by itself for days, it can perform all the tasks that a human would otherwise be doing. It can refocus, it can find infected cells and zoom in, and when it detects a release of parasites it can change its imaging modality by going into a high frame-rate acquisition. And when the release has finished it can search around in the culture to find another cell to monitor automatically," said Cicuta. "We also want to integrate a technique called an optical trap, which uses a laser beam to grab cells and move them around, so we can deliver the parasites to the cells ourselves and see how they invade."

"So far, we've been able to gather over 50 videos of infections, which my PhD student Alex Crick has processed to show very clearly that the RBCs undergo large changes in shape when the merozoites touch them. We've also seen very strange shape changes just before the parasites come out of the cells, and we want to see whether this has a bearing on the parasites' ability to infect



The parasites attach to and enter red blood cells to develop and multiply

subsequent cells."

During the development of the microscope, the team discovered variability in the way the infected RBCs behave before they burst. "It's important to know that there isn't just one story. The only way to find this out is to look at many cells, which this system allows," said Lew. "It's a new level of data that allows us to get experimentally significant results, and better understand the diversity of the merozoites," Cicuta added.

Used in conjunction with other tools such as fluorescent indicators and molecular biological tools, the new technology will allow Tiffert and Lew to test their hypotheses about the pre-invasion stage of the disease. They hope to determine the critical steps, which could provide clues as to how to stop an infection. "This microscope is an extraordinary new tool that has potential for use across a huge field of biological problems involving cellular interactions," explained Lew.

"It may provide a route to designing effective antimalarial drugs, reducing invasive efficiency and decreasing mortality," said Tiffert. "The automation we have achieved with this microscope will also be very important for future testing of malaria drugs and vaccines," added Cicuta.

A visionary initiative

"The Physics of Medicine Initiative has been essential to our work," said Cicuta. The University formally established the Initiative in December 2008 through the opening of a new purpose-built research facility adjacent to the Cavendish Laboratory, funded by the University and The Wolfson Foundation. The goal is to break down traditional barriers that have tended to limit interactions between researchers in the physical and biomedical sciences.

"I met my collaborators through a Physics of Medicine symposium, and the new building is the only place in the University where this type of research can be done," added Cicuta. "It's set up for safe handling of hazardous biological organisms like *P. falciparum*, and also has the facilities to design hardware for our advanced microscopes. This work is exciting because it's interdisciplinary. By applying physics to the knowledge biologists have been developing for many years, we can make very fast progress."

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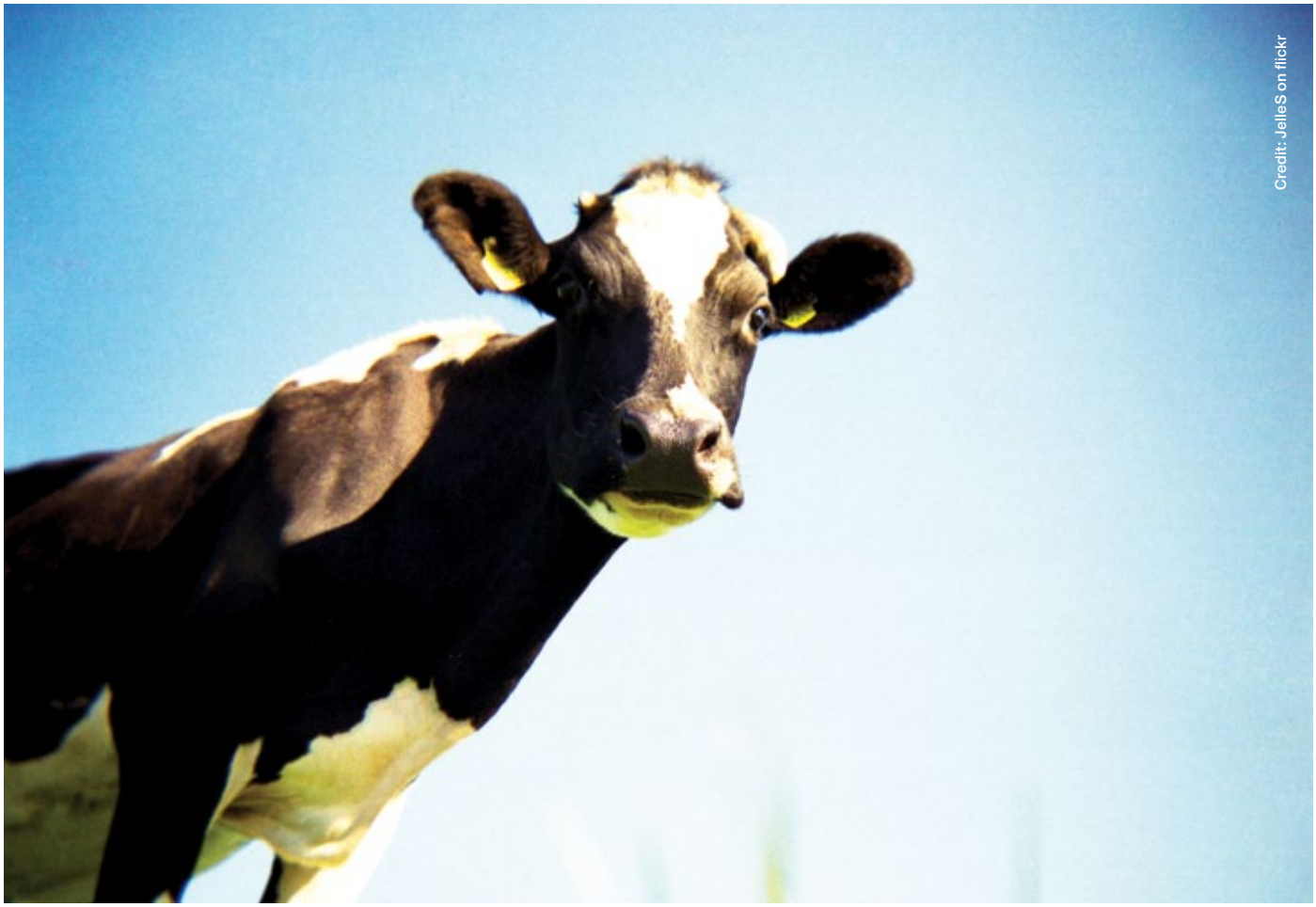

Credit: JelleS on flickr

March of the superbugs

Scientists who recently discovered a new strain of superbug have now tracked its transmission between animals and humans.

Every so often, research laboratories and hospitals testing patients for the superbug methicillin-resistant *Staphylococcus aureus* (MRSA) have come across an oddity: a strain that appeared to be MRSA because it was resistant to antibiotics but one that tested negative with the 'gold standard' molecular test. The quirky cases were so infrequent that they were usually filed away for future analysis or disregarded. Until, that is, PhD student Laura Garcia-Alvarez from Cambridge's Department of Veterinary Medicine had the tenacity to look a little further at a bacterial strain she had spotted in cows' milk.

MRSA first appeared in 1961 and epidemic strains of this difficult-to-treat bacterium have since spread worldwide in hospitals and the community. In the farming world, MRSA causes bovine mastitis – an infection of cows' udders – affecting both animal welfare and milk yields.

Garcia-Alvarez was working with Dr Mark Holmes on bovine mastitis when she came across one of the 'curious anomalies'. The strain was resistant to antibiotics but in the standard molecular test was negative for the presence of *mecA* – the gene responsible for methicillin resistance. She had the isolates retested and then sequenced at the Wellcome Trust Sanger Institute.

It turned out that she had discovered a new strain of MRSA. Its antibiotic resistance is carried not by *mecA* but by *mecC*, a gene that is so genetically dissimilar to *mecA* that it can't be picked up by the standard molecular test used to define MRSA but only by DNA sequencing.

As Holmes and Garcia-Alvarez began to spread the information to colleagues around Europe, it soon became clear that this phenomenon was not confined to cows: others had found the unusual samples in humans. "We started to get calls from hospitals and research groups who had come across a small number of human MRSA strains that behaved differently," said Holmes. "Within a few weeks, we had a further 50 isolates. This meant that what we were looking at was a human problem too."

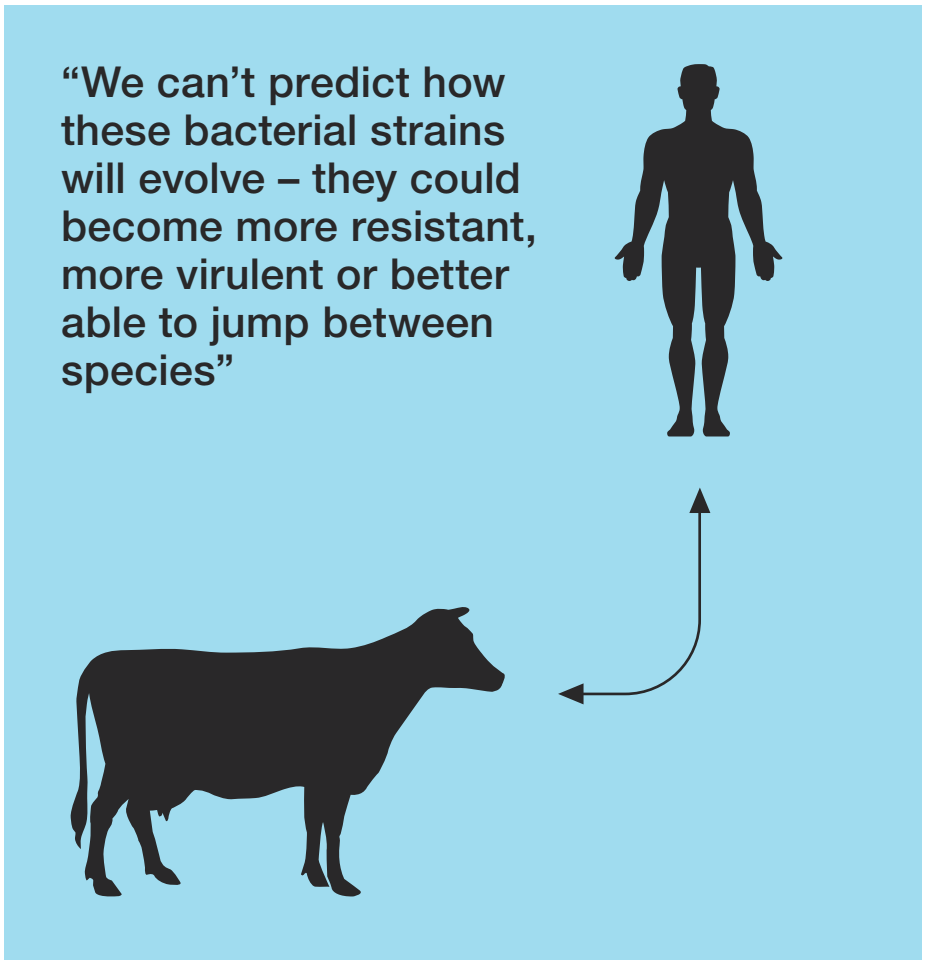
Garcia-Alvarez, who at the time was a student on the Department's postgraduate training in infectious disease dynamics programme, described how finding the same new strain in both humans and cows was worrying, although no cause for immediate alarm: "Pasteurisation of milk will prevent any risk of infection via the food chain. In the wider UK community, less than 3% of individuals carry MRSA – typically in their noses – without becoming ill."

"Nonetheless," added Holmes, "MRSA presents a major challenge to the control of infectious diseases. Finding a new strain – studying its prevalence, how it confers antibiotic resistance and how it's transmitted – can tell us enormous amounts about the origins and evolution of antibiotic resistance."

New understanding

Since the discovery, Holmes' team has been investigating the prevalence of the strain in human and animal populations – and the potential for passing the strain between species – in partnership with Cambridge's Department of Medicine, the Sanger Institute and the Moredun Research Institute (Scotland), and funded by the Medical Research Council.

One of their first steps was to develop a better genetic test, one that also detected the new strain. The timing was fortuitous.



Moves to help hospitals identify MRSA more quickly have resulted in the development of automated systems based on genetic testing. Because the standard genetic test does not detect the new strain, the scientists have now developed a protocol that will pick up both strains.

Moreover, their recent research has shown that additional MRSA strains have emerged that possess other mechanisms of antibiotic resistance: "We've found about 40 human MRSA isolates that don't have a *mecA* or a *mecC* gene, and we are trying to establish why these are resistant to methicillin-family antibiotics. In retrospect, it was incredibly lucky that the original isolate we investigated happened to have a genetic variation in a known gene that could be picked up by whole genome sequencing."

£170 million

Mastitis costs the UK dairy industry around £170 million per year

To identify how *mecC* confers antibiotic resistance, Holmes collaborated with Professor Alexander Tomasz at Rockefeller University, New York. They discovered that the gene is more resistant than *mecA* to cefoxitin (one of the newer classes of antibiotics): "Inappropriate use of antibiotics in human and veterinary medicine has favoured the selection and growth of antibiotic-resistant microorganisms," explained Holmes. "Our finding suggests that an increased use of this drug may have driven emergence of the new strain."

"We also now know that the new strain is found in almost every species that we've studied, including domestic cats and dogs, wild rats, deer, a rabbit, a common seal, sheep and a chaffinch. The bacterium may have lost factors that restricted it to certain species, or gained pan-host virulence factors that make it better able to colonise multiple species. We need to know how and why this has happened to understand the emergence of bacterial pathogens from animals and their dissemination into human populations."

Now, their latest research has tracked transmission of the superbug, providing the first direct evidence of transmission of the new strain between livestock and humans.

The researchers capitalised on a growing trend to use increasingly rapid and affordable DNA sequencing for tracking the transmission of pathogens. This technique is helping scientists to look for differences at the level of single letters in the genetic code as a means to map the direction of infection – from patient to patient, and from one animal species to another. The team investigated two cases of *mecC* MRSA in Danish farmers. The strains circulating in the farmers' livestock and those isolated from the patients only differed by a small number of letters – strong evidence that the farmers had acquired their infections from their animals, in one case a sheep and in another a cow.

"The ability to confirm animal-to-human transmission in virtual real time using this technology can't be underestimated," said Holmes. "High-throughput DNA sequencing is going to revolutionise clinical microbiology by enabling targeted epidemiological follow-up and infection control."

Nearing the precipice

Mastitis is the most common infectious disease of dairy cattle, affecting the welfare of cows and, according to one estimate, costs the UK dairy industry around £170 million per year. Its control and treatment relies on the use of millions of doses of therapeutic and prophylactic antibiotics every year. "Our research on MRSA is pointing to the fact that although we are not on the precipice of having the whole system collapse through selection of bugs that are even more resistant or having husbandry systems that make it impossible to eliminate them, we are closer to the precipice than we would like to be," said Holmes. "As it is, *S. aureus* is considered impossible to eliminate in dairy herds – you have to live with it once you've got it. "Farmers and veterinarians are in a constant battle to improve the health of dairy cows, yet farming cannot be sustained at these levels if it is generating these types of resistance. Moreover, we can't predict how these bacterial strains will evolve – they could become more resistant, more virulent or better able to jump between species."

Holmes views the interface between veterinary medicine and human medicine as crucial to understanding infectious diseases such as MRSA: "There is very little research on *S. aureus* mastitis in cows in comparison to research into it as a human pathogen, and yet now we're beginning to see exactly the same organism being found in people and in cows. This means that we should be thinking about the epidemiology of disease control and the development of antibiotic resistance in both species. Understanding how new strains emerge will help us to understand the growing public health problem of antibiotic resistance."

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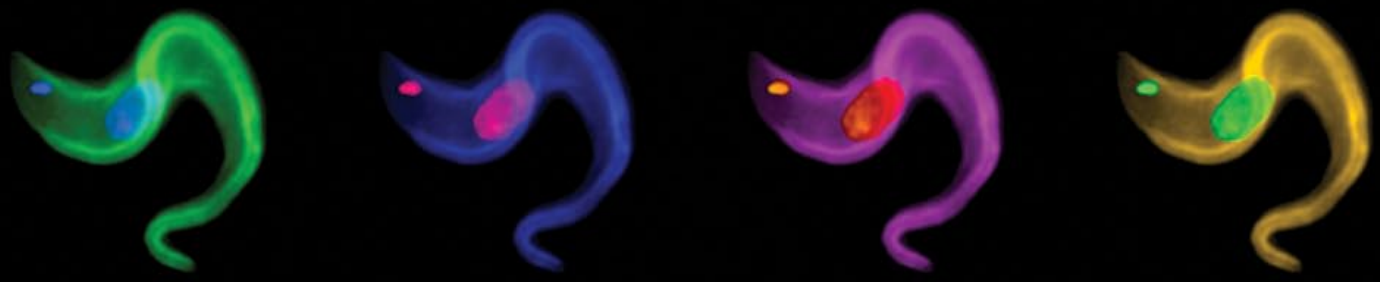
Sleeping sickness by stealth



Credit: Mark Field and Susan Wang

Image
Trypanosoma brucei use a changing cloak of VSG coat proteins to confound recognition by the human immune system

New research is helping to unveil how the parasite that causes sleeping sickness uses stealth tactics to escape detection by the human immune system.

Stealth is a well-known concept in military tactics. Almost since the invention of radar, the hunt began for counter-technologies to hide aircraft and missiles from detection – most successfully by modifying the composition and shape of surfaces to confound detection. In a biological parallel, the African sleeping sickness parasite *Trypanosoma brucei* also has a stealth-like trick for altering its surface to confound recognition by the human immune system.

Trypanosomes are covered in some 10 million identical proteins called variant surface glycoproteins (VSGs). Although VSGs are well recognised by the immune system, trypanosomes can rapidly and repeatedly change every single one of these coat proteins, just as the rumblings of an immune response against the first coat have begun. In this way, the parasite can effectively 'disappear' again and again, deflecting the immune response to something that has essentially become an echo.

A complex mechanism of gene control underlies the process that allows trypanosomes to switch coats. Part of this mechanism has now been revealed in recent research by Cambridge parasitologist Professor Mark Field and colleagues from the USA, UK and Europe.

The finding has implications for treating African sleeping sickness, one of the 'neglected tropical diseases' – those that are caused by infectious agents that are endemic to low-income populations in Africa, Asia and the Americas, where treatment may not be universally available or is poor. Sleeping sickness threatens millions of lives in sub-Saharan countries and, because it also affects cattle, is a major contributor to economic hardship. Currently there is no vaccine.

At the heart of *T. brucei*'s switching mechanism is a set of genes, possibly as many as 2,000, encoding the VSGs. Only a single VSG gene is active at any one time – ensuring that the coat contains only a single protein. All other VSG genes are inactive or silent.

"The active VSG gene is within a site lying close to the end of the chromosome, while all the silent genes are elsewhere in the parasite genome," said Field. "When switching occurs, the genes become rearranged and a gene from the silent archive is moved into the expression site. When this one is expressed, new coat proteins are moved to the cell surface to replace the old coat."

The researchers have discovered a protein, NUP-1, which helps to maintain the silent archive, as Field described: "The basis of gene silencing is epigenetic. In other words, it's not written in the DNA per se but is the result of protein 'decorations' called chromatin that either block or allow gene expression. NUP-1 is one of the proteins controlling epigenetic gene silencing."

In multicellular organisms, a key regulator of chromatin remodelling is a protein called lamin, which forms a network across the inner lining of the cell's nucleus. Until the discovery of NUP-1, an equivalent protein was unknown in plants, fungi or single-celled organisms. NUP-1 not only performs lamin-like functions – suggesting that the mechanism NUP-1 controls is probably an ancient process shared by organisms as diverse as humans and their parasites – but, excitingly, its discovery also opens up new possibilities for eradicating *T. brucei* by controlling coat switching.

"Without NUP-1, silenced genes are no longer constrained, and increased VSG switching happens," explained Field. "If we could inactivate NUP-1, the parasite will probably exhaust the VSG repertoire or damage the surface coat so that it's no longer effective as a barrier. This may finally be one route to penetrating the stealth cloak of *Trypanosoma brucei*."

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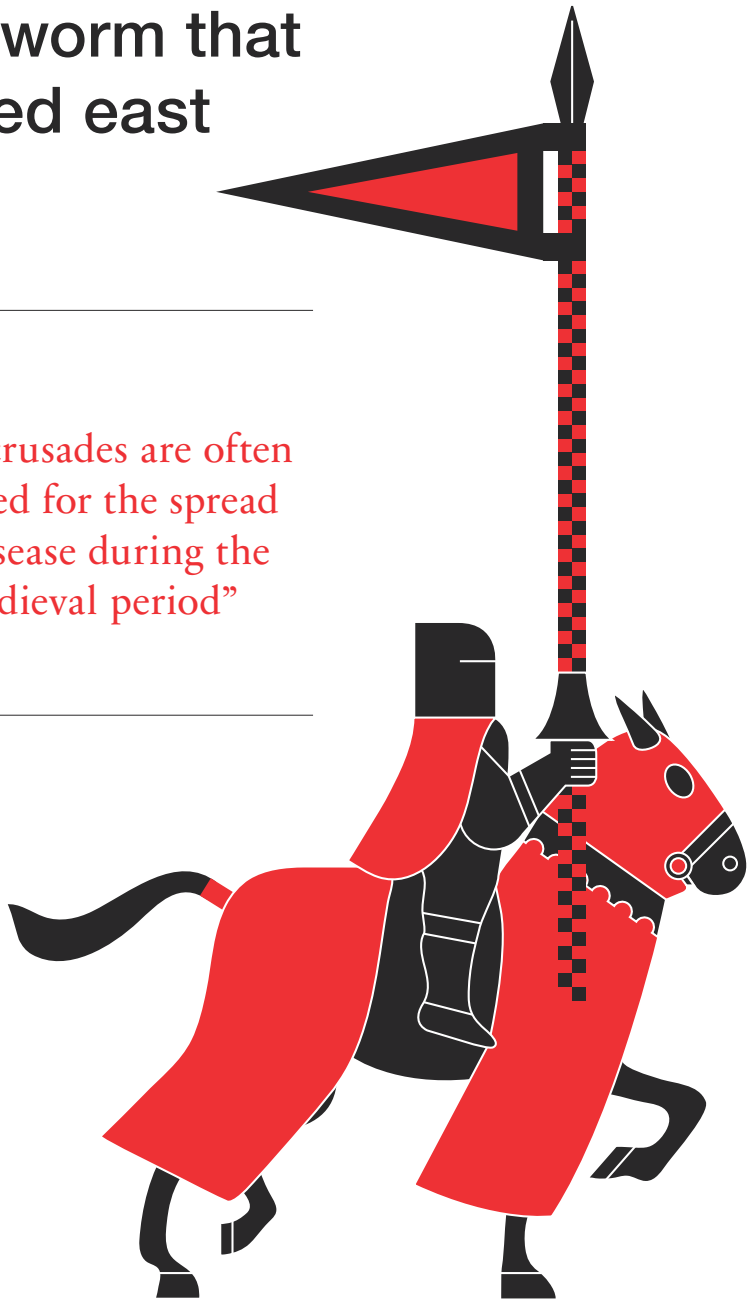
The worm that turned east



"The crusades are often blamed for the spread of disease during the medieval period"

The contents of crusader latrines are helping researchers probe the history of parasite infections in humans.

When the crusaders of the Order of St John first built a 35-latrine toilet complex in the medieval city of Acre, they could scarcely have considered that researchers would be sifting through its contents 900 years later. Yet the 13th-century latrine soil is providing another chapter in understanding the long history of our relationship with intestinal parasites.

Biological anthropologist Dr Piers Mitchell has been extracting sediment derived from decomposed faecal material and analysing it under the microscope. Long after the many different types of parasites have perished, their tenancy in the intestine of their human host can be deduced by the presence of their eggs, now hundreds or even thousands of years old.

There is a growing body of research worldwide that attests to the fact that parasitic worms have been uninvited guests of the human intestine for millennia. It's a relationship that is still as strong as ever: today, 740 million people in the tropics have human hookworm according to estimates by the World Health Organization.

One aspect that has captured the attention of researchers is the ability to trace ancient human migrations through the parasites the migrants took with them. As one example, the sequential waves of peopling of the Americas has been timed through the hookworms that infected them. Such research also provides an opportunity to look back to when and how parasites came to cause disease in humans. "We can then understand what impact these infections have had, and will continue to have, upon our evolution," explained Mitchell.

The crusades were arguably the greatest migration event that took place in medieval Europe. In the 12th and 13th centuries, hundreds of thousands of Europeans travelled to the eastern Mediterranean on military campaigns, pilgrimage and to trade.

"The crusades are often blamed for the spread of disease during the medieval period," explained Mitchell, whose work was funded by the British Academy. "But only limited research has investigated which diseases might have been spread, in which direction, eastwards or westwards, and what impact this may have had upon the endemic patterns of disease."

When Mitchell analysed the crusader latrines, he was able to identify the eggs of roundworm, whipworm, beef/pork tapeworm, dysentery and fish tapeworm. He explained why the latter was of particular interest: "Fish tapeworm is found in northern Europe where it infects humans when they eat salted, smoked or dried fish. It's not found in the Middle East, probably because the environment doesn't seem to support the lifecycle of the worm."

"We were able to confirm that the parasite was not there before the crusades. We believe the crusaders brought the parasite with them when they travelled to the eastern Mediterranean with fish tapeworms in their intestines. This is a great example of how migrations in the past can move diseases around the planet. Sometimes they take hold there and become endemic, and sometimes they don't."

Mitchell now plans to extend his research even further back in time, focusing on the wider Fertile Crescent – a region that stretches from Jordan to Iran. Here some of the earliest civilisations developed during the past 10,000 years.

"There are theoretical arguments that when our ancestors were hunter-gatherers perhaps they had fewer parasites because they kept moving on. Once they settled and lived in the same places did that make them more predisposed to reinfecting themselves with their parasitic diseases?"

His new research will trace the history of parasitic infections in the Middle East from 9,000 BC till Roman times, and will ask such fundamental questions as: when did intestinal parasites first become common in humans? Did the introduction of farming practices such as irrigation expose people to new species of parasite? And even, what impact did the invention of the humble toilet seat have on public health?

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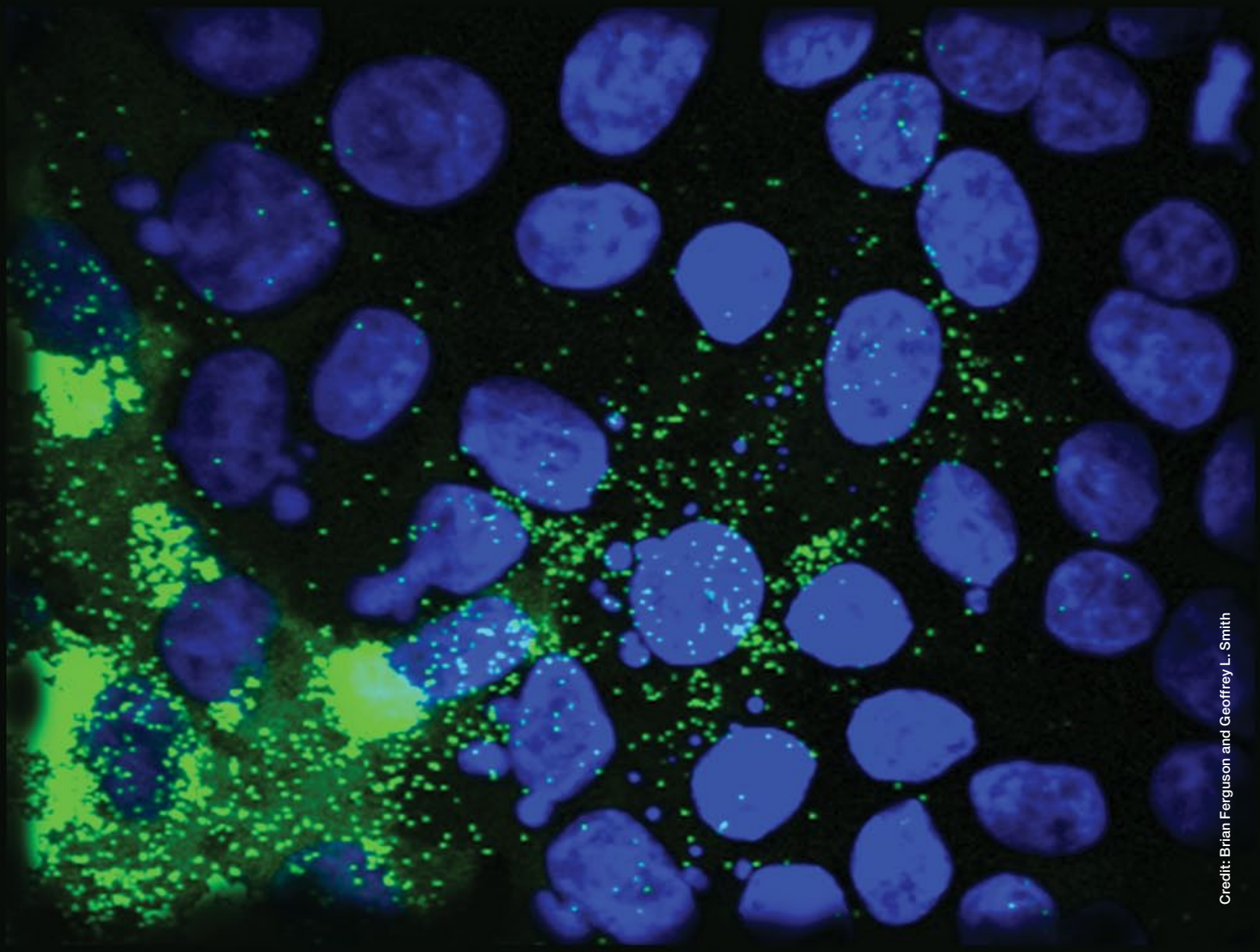


Credit: Brian Ferguson and Geoffrey L. Smith

Harnessing the power of the virus

Images
Above: Individual vaccinia virus particles (green) can be seen spreading from the bottom left to the top right on a layer of mammalian cells (blue); the bright green patches in the cells in the bottom left are 'factories' where new viruses are being made

Right: A cell (red) infected with vaccinia virus particles (green) is shown pushing away individual virus particles (boxed) on actin projections to infect new cells

The clever ways viruses have for evading our immune system are under scrutiny. Exposing their secrets is leading to a new armoury in our fight against disease.

For millions of years viruses have been evolving ways to outsmart our immune system so they can replicate inside our bodies and spread. In the process many cause infectious diseases, ranging from the common cold and influenza to hepatitis and AIDS. Now, by gaining a greater insight into their complex mechanisms, virologists are manipulating viruses to work for, rather than against, us.

"We're trying to understand how our immune system works – how it responds to and fights pathogens, particularly viruses," said Professor Geoffrey L. Smith, Head of the University's Department of Pathology. "If you want to study the immune system, you study the pathogens. Viruses have known how our immune system works for millions of years, and have developed many methods to overcome it. But we are only now discovering these secrets."

Smith leads a team of virologists focused on vaccinia virus, from which vaccination gets its name, and the one used to wipe out smallpox. "The virus has about 200 genes, and amazingly about half of these code for proteins that block the host immune response. This is a fantastic resource for understanding our immune system," said Smith.

Building better vaccines

"The smallpox vaccine was very successful – indeed it was the only vaccine that has ever eradicated a human disease," said Smith. "By generating an immune response it provided protection against devastating illness. But it was imperfect in terms of safety, causing various complications and, in rare cases, death. If we're going to reuse vaccinia for other vaccines, we need to improve its safety."

Working in Bernard Moss's laboratory in the USA in the 1980s, Smith and fellow postdoc Michael Mackett developed methods to genetically engineer vaccinia so that a gene taken from another organism could be inserted into it. The aim was to make vaccinia produce foreign antigens – molecules against which antibodies are produced. "Now we can insert the gene encoding the desired antigen from any pathogen – bacteria, virus, or parasite – into vaccinia, and get vaccinia to express the antigen and present it to the host immune system. This initiates an immune response, making the host immunised against the pathogen from which that gene was derived."

Vaccinia is now being developed into a variety of vaccines, which are undergoing clinical trials against diseases including AIDS and tuberculosis. "It's a generic platform that we can manipulate and target against different diseases," said Smith. "But we want to end up with a vaccine that is safer and more potent. The platform can be improved by removing genes that enable the virus to block our immune system, if we can work out what these are."

Detecting infection

Smith's team is exploiting vaccinia to understand the complexities of our immune system. Finding the molecular signals that tell a cell it is infected has been a goal of immunologists for decades. In an article published in the new online journal *eLife* in December, Dr Brian Ferguson, recently appointed to University Lecturer in the Department of Pathology and a former member of Smith's lab, describes a newly discovered mechanism by which the immune system detects invading DNA viruses.

"We have been looking at how the body knows it's infected by a virus," said Ferguson. "To fight off an invading virus, we have to know it's there. We have systems in all our cells to sense invaders and to respond by producing danger signals. We've discovered that an already well-characterised protein called DNA-protein kinase (DNA-PK) acts as the initial sensor to detect infection."

In its role as a 'pattern recognition receptor', DNA-PK senses when viral DNA is present in the body and sounds the alarm, telling the body to mount a rapid inflammatory response. "The DNA-PK works by binding to the foreign DNA it detects in the cell, and initiating a sequence of signalling events culminating in the production of molecules that amplify the body's response to the infection," added Ferguson.

"We've also discovered how vaccinia inhibits the immune system by interfering with DNA-PK," said Smith. A parallel investigation by PhD student Nicholas Peters, conducted in Smith's laboratory while at its former Imperial College London base, studied a protein made by vaccinia called C16. "We knew if we removed the gene coding for C16, vaccinia became less virulent," said Smith. "Nick's project was to understand how this worked. He tagged the C16 protein with a marker, introduced it into cells, and captured the molecules C16 bound to in the cells."

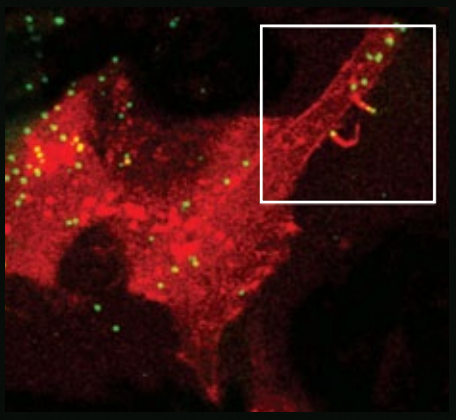
"Remarkably, C16 bound to two proteins that were part of the same DNA-PK complex that Brian had found was sensing virus invasion," said Smith. "This showed the additional biological significance of DNA-PK in restricting virus replication, because the virus has evolved a mechanism to prevent the triggering of an immune response. This explained why removal of C16 from vaccinia made it less virulent".

> "It's an arms race that has been going on for millions of years"

"Understanding the ways viruses have chosen to block our immune response is also useful because it shows us how to develop anti-inflammatory therapeutic agents," said Smith. "Diseases caused by excessive inflammation like rheumatoid arthritis derive from the inflammatory response not being properly regulated. Pathways activated by sensors like DNA-PK may be switched on all the time. Targeting such pathways would regulate the inflammatory response."

Knowledge is power

While our understanding of viruses grows, the emergence of new strains poses an ongoing threat to animal and human health. "It's our own fault for creating niches that viruses can occupy," said Smith. When humans existed at low population densities, viruses like variola (the cause of smallpox) and measles couldn't persist in man. They induced long-lasting immunity in their hosts and, with insufficient numbers of non-immune hosts to infect, they died out. But once population densities increased, these viruses could constantly be passed to new hosts and great epidemics



ensued. Smallpox killed 300 million people in the 20th century alone.

"Viruses are constantly evolving new ways to evade our immune system, and we need to understand their fundamental infection mechanisms, and ultimately how they kill people," said Ferguson. "It's an arms race that has been going on for millions of years. The human body is evolving new ways of detecting and fighting viruses, but at the same time the virus is evolving new ways to inhibit those mechanisms."

Advanced gene-sequencing technologies are giving immunologists a much clearer understanding of both human and viral DNA. "Sequencing an entire viral genome used to take years. With new technology we can do it in days," said Ferguson. "This will help us better understand how they mutate and evolve. And sequencing our own genome will help us to find out why some people are more susceptible to disease than others, and how different people will respond to a vaccine. These new technologies are an extremely powerful tool to understand the interactions between the virus and the human body."

"A major drive is to develop vaccines based on DNA or DNA-containing viruses that express antigens specific to different pathogens," said Ferguson. "If we can contribute to a better understanding of how existing vaccines work, we will be able to improve them. Our long-term goal is to make better vaccines and understand how to develop anti-inflammatory therapeutics, learning from the mechanisms viruses themselves have evolved."

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Credit: Jacqueline Garget

Inside out

Meeting Professor Deborah Howard

Swirling mists, slinking cats, friendly locals and "miles" of archive shelves. That's how Deborah Howard remembers Venice in 1970, a city where she first lived when studying its architecture for her PhD, and a city that has sustained her research interests for the past 43 years: "It was magic. I got addicted so quickly."

As Professor of Architectural History in the Faculty of Architecture and History of Art, her research focuses on the history of buildings. But she looks beyond bricks and mortar to the people who commissioned them, built them and lived in them. Not only is she fascinated by how buildings were used, but also how they related to the townscape of the city and, more widely, how they were shaped by influences from far-removed lands.

So, to research her book *Venice and the East: The Impact of the Islamic World on Venetian Architecture 1100-1500*, she travelled to the Near and Middle East, seeking out the places where Venetian merchants traded. "The interaction between Venetian and Muslim merchants was very important for shifting goods such as spices and textiles from central Asia into Europe. I wanted to see what the Venetians had seen, and to understand how this related to influences on Venetian architecture."

And, in her latest book, *Venice Disputed*, she turned her attention to a prominent character in the creation of the Venice we see today: the 16th-century Senator Marc'Antonio Barbaro, whose architectural legacy includes his beautiful villa designed by Palladio, the Rialto Bridge and the famous star-shaped fortified town of Palmanova. Her painstaking analysis of his public and private life paints a compelling story of the political process and bitterly contested debates that underpinned Venice's urban development 500 years ago.

Professor Howard is one of a trio of Renaissance scholars which has recently been awarded over €2.3 million by the European Research Council to study 'Domestic Devotions: The Place of Piety in the Italian Renaissance Home'.

Q What's the point of your research?

A I find buildings fascinating because they are settings for human activity. They were built for a purpose and had to perform a function. Of course the design is incredibly important and interesting, but the design responds to certain conditions – social, geographical, economic, physical – and I want my research to integrate this complex matrix with architecture, to bring buildings to life. Architectural culture is one of our great resources. It's important for civilisation and civic values, and it's an economic asset. The more we understand it, the better for society.

Q What might others be surprised to learn about you?

A I've climbed all 283 Munros [mountains in Scotland with a height over 3,000 ft]. It took 27 years and is by far the most challenging thing I've ever done in my life.

Q Ever had a Eureka moment?

A When you are tracking down documents in the archives it's like time travel, detective work. When you actually hold the piece of paper that 500 years ago someone wrote, cried over, spilled their wine on, you get to know personalities, and you delve deeper. It's really like being a sleuth. An awful lot has survived in the Venetian archives – literally miles of shelves – and Eureka moments happen when you make unexpected connections between pieces of evidence.

Q What is the best piece of advice you've ever been given?

A My husband said I must write a book for every child we had. I wrote a book before each of my two children, and have continued writing ever since, when at first I might have simply become an earth mother and made jam. I think that was a very important piece of advice because I've had the most wonderfully exciting career. I've loved every minute of it.

Q Describe your childhood self.

A Diary-writer, outdoorsy, avid photographer. Even as a child I was desperately interested in places, landscape and travel. I would write detailed diaries with photos and maps of everything we saw. I got deeply involved in anything I did, inventing intricate games that would go on for weeks all through the summer holidays. My father had five sisters and they were wonderful childhood role models for me – mountaineers, artistic, musical and fun.

Q What is your favourite research tool?

A My camera.

Q Who or what inspires you?

A Risk takers. I've always like doing things that are a little bit dangerous, either intellectually or physically. I like breaking out of what people expect you to do. I'm not a rebel but I like to stretch the boundaries of my subject, yet to keep it rooted in proper evidence.

Q What skills do you draw on to carry out your research?

A My work has tried to extend architecture outwards in an interdisciplinary way. I've needed to learn to read 16th-century Italian documents but also to understand building construction and materials, cross-cultural exchange, politics and society.

Q How would you like to be remembered?

A I hope, as somebody who was loyal and inspirational to their students. That would be my greatest aim. They have the future of the subject, not me; they have the new ideas and are going to take the field in new directions. They are fabulous, and very important to me.

Forget walking

Tiny insects jump on water

An insect not much bigger than a grain of rice is able to repeatedly jump on the surface of water using specialised paddles on its hind legs, new research reveals.

While eating his lunch near a pond in Cape Town, South Africa, Professor Malcolm Burrows from the Department of Zoology heard noises coming from the water, and observed something he had never seen in his 48 years of research – an insect jumping across the water's surface.

He collected the creatures – which turned out to be pygmy mole crickets – and brought them back to his lab to analyse them jumping using a high-speed camera. It was there that he, along with engineer Dr Gregory Sutton, discovered the unusual manner in which these 5 mm long insects cross the water adjacent to their muddy burrows.

The pygmy mole cricket relies on its powerful hind legs to accomplish the feat. As they push downwards, specialised spring-loaded paddles and spurs fan out to increase the surface area, propelling a small ball of water downwards and launching them upwards into the air. Once the thrust has been applied, the paddles then rapidly snap closed to reduce the drag.

"For small insects, water can be a deadly, sticky trap; water grabs and holds an insect, offering it as an appetising snack for an alert fish," Burrows explained. "Other animals use surface water tension, keeping a small layer of air between their feet and the water. However, if their feet get wet, they will be pulled into the water and drown. Pygmy mole crickets turn the stickiness of water to their advantage and use this property to enable jumping."

The researchers believe that the pygmy mole crickets' unique technique for jumping on water could be used to inform the development of small robots that could be used in water. Burrows added: "If we want to make small robotic vehicles that move under water, this is how we would have to design propellers or oars."

Credit: Malcolm Burrows

Film available online

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