βluesci

Cambridge University science magazine

Lent 2016
Issue 35

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FOCUS

Global Issues: Malaria

Vaccination · Drug Resistance · Ghost Virus

Titan Arum · Decarbonisation · Crop Diversity

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BlueSci was established in 2004 to provide a student forum for science communication. As the longest running science magazine in Cambridge, *BlueSci* publishes the best science writing from across the University each term. We combine high quality writing with stunning images to provide fascinating yet accessible science to everyone. But *BlueSci* does not stop there. At *www.bluesci.org*, we have extra articles, regular news stories, podcasts and science films to inform and entertain between print issues. Produced entirely by members of the University, the diversity of expertise and talent combine to produce a unique science experience.

Issue 35: Lent 2016

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Cover Image: Jessica McHugh

Global Issues

In the last century, the world has seen many changes. The human population size has doubled to over 7 billion since the 1970s, and is growing at a rate of approximately 200,000 per day. Advances in science and technology have boomed and communication and travel have never been easier. However despite these advances, today we face many global issues.

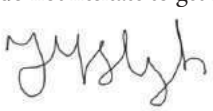
The Focus of this issue is on malaria, a global killer whose dark history has been marked by death and failed eradication attempts. The rise of drug-resistant forms threatens to undo the great strides we have made over the years in the control of this disease. As discussed by Arthur Neuberger, resistance to drugs is not limited to malaria. The emergence of antibiotic resistance has the potential to undermine modern medicine, taking us back to a time when simple and treatable infections become lethal. Controlling infectious diseases is not only important for an individual's health, but for that of the whole population. Misuse of antibiotics by one individual risks the health of another. Similarly, an individual's choice not to vaccinate can also help spread a disease. Preventable diseases such as whooping cough and measles are also on the rise due to a decrease in vaccinations. Caitlin Stewart highlights new research into the best way to tackle this "anti-vaxxer" movement.

Deadly epidemics, such as Ebola, are also a global threat, with its recent outbreak killing over 10,000 people. Although it is now largely under control, such epidemics can bring their own unforeseen problems. Bethan Clark describes the newly termed post-Ebola virus disease syndrome, which now haunts an already devastated community.

It's not just our health we need to be concerned with. Last year, world leaders met in Paris to discuss climate change, one of the biggest topics of our time. 2015 was the hottest year on record, with eight months being the warmest for their specific months. Melting ice-caps, droughts, floods and other extreme weather patterns are some of the consequences now facing us. A shift towards renewable energy is an obvious way forward, but as Lachlan Jardine points out, the route towards decarbonisation is not necessarily an easy one.

To be able to adapt to these changes, we need to secure not just our energy, but also our food sources. The importance of crop diversity is highlighted by Janina Ander. Preserving the world's biodiversity is another pressing challenge. There are many amazing and bizarre lifeforms, feeding our curiosities and inspiring us in both art and science, as discussed by Hannah Wayment-Steele.

More than a decade ago, the Titan Arum first bloomed in Cambridge. The same year, BlueSci printed its first issue. Eleven years on, the Titan Arum blooms for us once more and BlueSci is still going strong. This is thanks to efforts of our writers, editors and producers who work hard on each issue. If you share the passion they have for communicating science, and would like to contribute to future issues, do not hesitate to get in touch!



Jessica McHugh
Issue 35 Editor

On the Cover

During the 1970s, the golden age of arcade games such as Space Invaders, Britain saw an average of 200 cases of malaria each year. The world has seen much change since then, with many strategies and drugs being adopted to combat this disease. Despite this, the rise in overseas travel has seen the number of cases increase to 1,500 every year. However, this pales in comparison to the over half a million people who are killed by malaria annually worldwide, with more children dying from this infection than measles and HIV/AIDS combined. 90% of these cases are in Sub-Saharan Africa, with poverty, lack of resources and drug resistance keeping these numbers high and difficult to eradicate. With half of the world's population living in malaria-risk areas, this disease continues to be a global threat.

The cover photograph overlooking Earth was tweeted last year by astronaut Terry Virts (NASA), commander of Expedition 43 on board the International Space Station, with the simple comment "#Earth" (July 2015). Although we may have travelled to the moon and back there is still much to learn about our own home. This unique world in which we live deserves our respect.

Jessica McHugh, Issue Editor

News

DANIEL J LAYTON

Gut bacteria key in diet interventions

A RECENT STUDY conducted at the University of Gothenburg shows a link between the effectiveness of dietary intervention and gut microbiota. Thirty-nine participants were asked to eat kernel barley bread for a period of three days and to replace it with white flour bread for another three days after a break.

Blood sugar levels improved during the kernel barley bread diet, but only in some of the participants. Sampling of the gut microbiota revealed a large prevalence of the bacteria *Prevotella* in patients who showed improved metabolic function. Recent findings further show that mice supplemented with *Prevotella* tend to have lower blood sugar on a high-fibre diet, suggesting a link between gut microbiota, diet and metabolic functions. Together, these results suggest an intricate connection between gut bacteria and dietary fibers in modulating several disorders linked to blood sugar, such as diabetes, cardiovascular diseases and obesity. Future studies are needed to confirm these observations.

The research group is currently studying the role of several bacteria in modulating metabolic responses to high-fibre diets by manipulating the microbiota profile of germ-free reared mice. The findings of this research could help to maximize treatment and prevention by combining individualized dietary recommendations and prebiotics supplements. The study is in line with an increasing number of research papers showing a relationship between the gut microbiome and several biological functions, although the cellular and molecular mechanisms involved are not yet fully understood. **CG**

PUBLIC DOMAIN

Transplants: survival of the wealthiest?

CANDIDATES FOR organ transplants may increase their survival rate by registering at multiple organ transplant centres. While this approach reduces waiting times, it was long suspected that it favoured wealthier patients who could afford the non-medical costs of this, such as travel and accommodation. Now, research presented at the American Heart Association suggests that wealthier patients have an advantage in waiting lists, undermining the principle that sickest patients should come first.

Researchers from Columbia University Medical Center analysed the United Network for Organ Sharing database, looking at adult patients registered for heart, lung, liver or kidney transplants. According to lead author Dr Raymond Givens, patients listed in multiple centres lived in areas of higher income and had higher socioeconomic status. Despite indications that they would have to face longer waiting times and were on average less sick at the time of registering that single-listed patients, they were in fact more likely to receive transplants and had lower death rates while waiting. Even after controlling for various differences between multiple and single-listed candidates, multiple listing had a significant effect in increasing the rates of organ transplant and survival.

The fairness of the organ allocation process has been put into question by this study. It also highlights the need for more volunteers for organ donation. While waiting lists increase yearly, donor numbers do not. The authors argue that the policy of multiple listing should be reviewed to ensure fair access to organ transplants. **AD**

Check out www.bluesci.org or @BlueSci on Twitter for regular science news and updates

Scientific research is conservative but could be accelerated, analysis finds

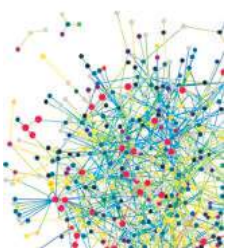
A COMPUTATIONAL STUDY of millions of biomedical articles has shown that research which avoids risk-taking, possibly encouraged by institutional and cultural pressures, could slow discovery in science. The two new papers from the University of Chicago sought to quantify the advantages and disadvantages of current research strategies, and uncover more efficient approaches.

In the research, networks were made by considering which molecules were studied. By adding a network link between two molecules every time they appeared together in research, a knowledge network was built up, with clusters of points representing individual scientific fields.

These networks could then be used to examine research strategy – did each article create a new link, hence reporting a novel relationship, or replicate a previously known link? Did new links connect molecules from different clusters? The efficiency of scientific research was also examined by determining how many experiments were necessary to uncover critical new knowledge.

The work showed that scientists are six times more likely to perform 'repeat' research than research which creates new links, a strategy which may be used to reduce personal risk. Furthermore, research within a field was found to grow more conservative over time, with researchers focusing more heavily on well-studied central molecules. However it was also found that innovative papers (which created new links) were more likely to be cited, and papers by the winners of the Nobel Prize and other prestigious awards introduced new molecules and relationships more frequently. In order to maximise efficiency, it was found that experiments should become riskier and seek more distant connections over time; by incentivising high-risk research and increasing publication of failed experiments, discovery could be accelerated.

"Scientists can often get trapped by concentrating on a small part of the network and spending large amounts of resources trying to solve the same problem," paper co-author, Andrey Rzhetsky, said. "This works for new fields, where many experiments have a high chance of successfully revealing a new connection. But much more effort, time and resources must be spent to make new discoveries in well-established fields. To maximize the pace of successful scientific advances, the best approach is to be adventurous and explore as broadly as possible." **RR**



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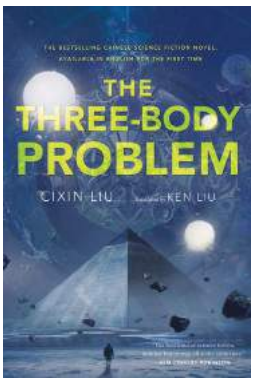
Reviews

The Three-Body Problem - Cixin Liu, translated by Ken Liu



Head of Zeus, 2015

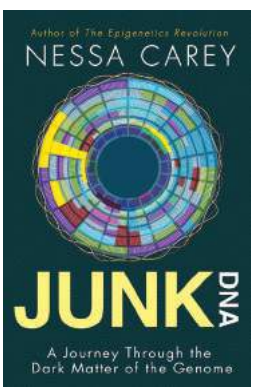
Having already reached cult status amongst Chinese audiences, *The Three-Body Problem* has stormed social media once more as the first ever translated book to win the Hugo Award. Controversial in context, the novel is set during the political turmoil of China's Cultural Revolution, where a secret military project is established to search for extra-terrestrial intelligence. Ye, a disillusioned young astrophysicist, initiates contact with an alien civilization that forever changes the fate of the human race. Unlike most alien invasion clichés this book has relatively few action/adventure elements to it. Instead, the character-driven narrative leads readers to slowly uncover the true nature of the alien civilization, in the style of any good old-fashioned mystery. The author's ability to convey his vision of the universe is impressive - reanimating notable historical figures from science and philosophy, and weaving them neatly into the narrative, is impressive. There are several 'Asimov' moments, increasingly rare in the genre, which really force one to think about the vast problems and possible consequences facing the scientific community. Although it may be a slow burner, this is no doubt a fresh and rewarding sci-fi that could be well worth your while. **SZ**

Plague Inc. - iOS and Android app

Ndemic Creations

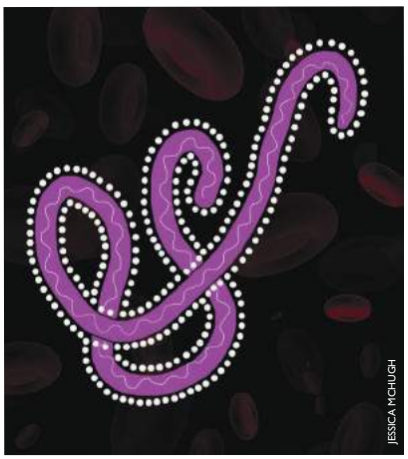
Plague Inc. – certainly the Ebola of the pandemic simulation genre that has (ironically) infected the App Store recently - seems simplistic at first. How hard could it be to design a deadly infectious disease to eradicate the human race?
It is, however, darkly satisfying to master each of the seven disease types, from simple viruses to the hunted nanomachines. They can be tailored to be more lethal and effective, which requires a balancing act between your plague's hardiness, severity and infectivity within a system that rewards experimentation as much as logic. Choosing what mutations to invest your accumulated DNA points on and when to adapt your disease to fight human resilience only enhances the sense of twisted pride you will no doubt experience once your little devil has "Killed more than smallpox". Victory is ensued once the last stubborn country succumbs and the world is left in anarchy.
With thousands of quirky world events to adapt to, hundreds of symptoms to evolve, and a diversity of pathogens to explore, there is a huge amount of replay value; whether you're looking for a 10 minute thrill as your disease mercilessly sweeps through Europe or an hour long strategic battle against humanity's last hopeful survivors. **LM**

JUNK DNA - Nessa Carey



Icon Books Ltd., 2013

The human genome is approximately 3 billion base pairs long, but only around 2 per cent of our DNA codes for proteins and RNA. Why on earth should our genome contain vast amounts of DNA that doesn't code for anything useful?
This is the question addressed by Nessa Carey, author of The Epigenetics Revolution, in her second book, Junk DNA. Throughout the 20 chapters of the book it becomes clear that the clichéd term 'junk DNA' is something of a misnomer. In fact, the abundance of non-coding DNA may be a key factor in human complexity, with adaptive functions such as regulating gene expression and 'insulating' coding DNA from damage. Much of the focus of the book is on the consequences of mutations in non-coding regions; uncovering the role of non-coding DNA in the development of genetic diseases, such as myotonic dystrophy, has been a crucial step forward for medical diagnosis and treatment. One of the most gripping revelations was that parts of our non-coding DNA are actually remnants of retroviruses that copied themselves into our genome millions of years ago.
Aimed at a general audience, Carey adeptly makes use of light-hearted analogies while guiding the reader through cutting-edge research in molecular biology. An exciting journey through the 98 per cent of the human genome that is so often overlooked, I struggled to put it down. If you're at all interested in genetics and DNA, be sure to put this book on your list. **SC**


JESSICA MCHUGH

The Ghost Virus

Bethan Clark explains the persistent effects of the Ebola crisis

With the media attention surrounding the situation having long since faded away, it is easy to forget about the West Africa Ebola epidemic, despite its magnitude. It dwarfed all previous outbreaks of the disease: a total of 28,607 cases and 11,314 deaths have been reported since the first confirmed case in March 2014, compared to the usual 500 cases each year. The actual figures are probably even higher, given the difficulty collecting data. However, with the epidemic apparently dying down in the three worst affected countries, Liberia, Sierra Leone and Guinea, the immediate danger has now dissipated – or so it appears.

Liberia was declared free of Ebola on 3rd September 2015 after a 42-day period without any new cases being reported, as was Sierra Leone on 7th November. Only a small number of cases continue to persist in Guinea. However, it seems the problems are far from over. Among the approximate 17,000 survivors, a serious unanticipated situation is emerging.

It began in the spring of 2015 when the May issue of the New England Journal of Medicine described the detection of the Ebola virus in the right eye of Dr Ian Crozier, a US doctor who had already recovered from the illness. In October 2014, he was discharged from hospital with no sign of the virus remaining in his blood, but two months later developed inflammation and very high blood pressure in his eye, causing blurred sight and pain. It was even reported that the colour of his iris changed from blue to green. His eye fluid was found to contain levels of Ebola virus even higher than had been in his blood. Over three months of treatment with steroids and antiviral drugs at Emory Eye Centre his vision improved – and his original eye colour returned – although the episode raised questions about the persistence of Ebola virus in the body. Crozier himself thought it was unlikely to be a widespread phenomenon, saying "The likely thing is that I'm an outlier," in a video released by Emory University.


PURPLEAPPLE428

Ebola can affect iris colour even if not present in the bloodstream

However, reports of survivors in West Africa experiencing a range of debilitating symptoms soon began to build up. The issues reported are many and varied; they include joint, muscle and chest pain, chronic fatigue, neurological problems, loss of hearing, sleep difficulties, severe headaches and memory problems. Visual problems, such as those experienced by Dr Crozier, are also common among survivors. In a WHO article, Margaret Nanyonga, a psychosocial support officer in Kenema, Sierra Leone said, "Some complain of clouded vision, but for others the visual loss is progressive. I have seen people who are now blind." More than half of the survivors in West Africa are thought to be experiencing some of these symptoms – which together have been termed post-Ebolavirus disease syndrome (PEVDS).

Symptoms similar to PEVDS have been observed after past outbreaks of virus. The long-term health consequences of the 2007 outbreak of Bundibugyo ebolavirus in Uganda were studied in detail: survivors provided information about their health status 29 months after the outbreak. The results showed that survivors of Bundibugyo ebolavirus infection were at significantly greater risk than people in the control group (i.e. people who had not been infected) for long-term health problems comparable to PEVDS.

The current problem is that the sheer number of survivors of the West Africa outbreak with PEVDS was completely unanticipated and it involves countries with healthcare systems that have already been stretched to the limit by the epidemic itself, so providing adequate care for survivors has been challenging.

So far, there is only one confirmed person for whom PEVDS has been life-threatening. In October 2015, British nurse Pauline Cafferkey was admitted in critical condition to a London hospital, after experiencing renewed symptoms of Ebola, which she had caught while working in West Africa last December. Her condition was

updated to 'serious but stable' and she is expected to remain in the isolation unit for some time. Medics who worked during the epidemic say there have also been cases like Cafferkey's in West Africa, but with patchy reporting it is difficult to estimate the scale of the issue.

The causes of PEVDS are poorly understood, revealing yet again how little we know about the virus. That said, the list of explanations can be narrowed down; currently there are three main possibilities. With such a range of symptoms, it is probable that PEVDS develops due to a combination of these potential causes. The first is that the symptoms may be the result of damage to cells and organs by the virus before it was brought under control. Another possibility is that the symptoms are a sign the immune system has turned on the body, mistaking native structures for the virus and targeting them.

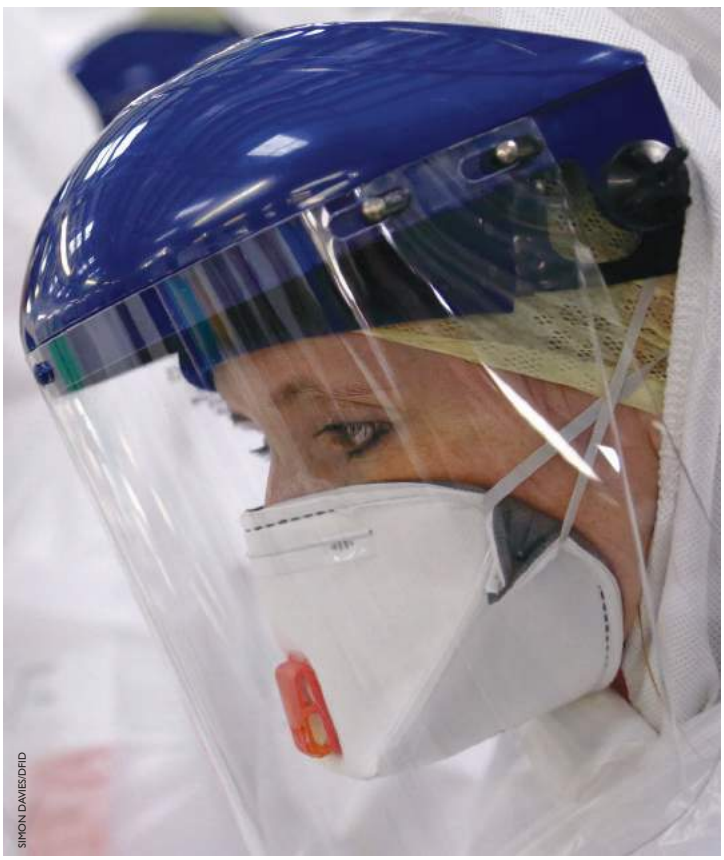
There is evidence both for and against this latter theory: one study found that the Ebola survivors with higher levels of antibodies (indicating stronger immune responses) were more likely to experience joint pain. Intriguingly, this parallels chronic fatigue syndrome, where the severity of the initial immune response plays an important role. However, blood samples obtained in the 2007 Bundibugyo study gave a more complicated picture, with Ebola-specific antibodies found in both survivors and control group.

The third possible explanation has been hiding in information we already have. The extremely high levels of Ebola detected in Dr Crozier's eye fluid demonstrated the ability of the virus to persist in parts of the body sheltered from the immune system. The presence of the virus in his – and other survivors' – eyes were therefore the likely cause of the inflammation that led to visual problems. The more we learn about persistence of Ebola virus in different 'immune privileged' sites in the body, such as the eye, the more likely it seems that this is the cause of many of the symptoms. Inflammation due to the continuing presence of virus in one such site, the central nervous system, could explain the chronic fatigue experienced by many survivors. When Cafferkey was readmitted to hospital she was treated for meningitis, which lends support to this theory, as meningitis is the result of inflammation of the brain. The testes are similarly protected from the immune system; it now seems that the virus can remain in human testes for at least nine months after it has stopped circulating in a person's blood, and is detectable in semen. As examples of viral persistence stack up, it might make sense to recognise PEVDS as part of the progression of Ebola, which would involve redefining the disease into an acute and chronic phase. Further evidence needs to be gathered to confirm whether this is an appropriate definition.

The persistent Ebola virus levels in localised sites in the body also have implications for survivor infectiousness. The Ebola virus is an RNA virus, meaning the transfer of its RNA is all that is required for a new infection. It seems the eye is not an infection risk to others, as viral RNA has not been found in tested tear fluids. However, this is not the case for other sites. A research team recently published evidence of a survivor in Liberia transmitting the virus sexually last March, due to its presence in his semen. Ebola virus RNA was also found in breast milk of survivor mothers, raising fears that children could be infected by breast-feeding: Sierra Leone's first Ebola survivor was warned not to nurse her baby until medics had confirmed there were no traces of the virus in her breast milk. Actual and potential new Ebola cases due to contact with survivors – who were previously thought to be non-infectious – could seriously hamper the final efforts to stamp out the remaining hotspots of the disease. The outbreak in West Africa continues to teach us new things about Ebola, and it is turning out to be a very costly education.

Health organisations around the world are coming together to tackle the Ebola virus

Risk of spreading the disease may remain after recovery



Bethan Clark is a 1st year Natural Sciences student at King's College.

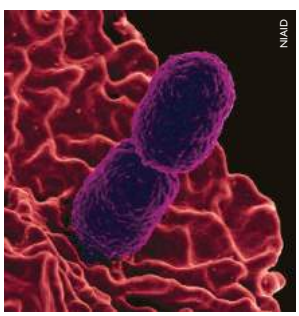
ROBYN CARTWRIGHT

Multidrug Resistance

Arthur Neuberger explains how increasing antibiotic resistance is a global threat that we breed inside ourselves

In an interview with the BBC on the emerging threat of antibiotic resistance, Professor Dame Sally Davies, the Chief Medical Officer for England, made clear that if global society does not take countermeasures against the spread of antibiotic resistance today, in 10 to 20 years from now, we all might be back to an 19th century scenario. In such a situation even basic infections as a result of routine operations would almost certainly be lethal, not to mention the inability to conduct most of our current cancer treatments. The World Health Organization ranks multidrug resistance (MDR) as one of the three greatest risks to human health, the others being climate change and malnutrition.

Scientists have discovered bacterial antibiotic resistance genes in DNA extracted from 30,000 year old permafrost sediments in Bear Creek, Canada, showing that drug resistance is certainly not just a recent evolutionary trend. By analysing these genes, they have demonstrated the striking similarity between current bacterial drug resistance genes and those of 30,000 years ago. What is new, however, is the increasing spread of multidrug resistant strains that are able to withstand specific antibiotics as well as complex cocktails. One major factor driving the increasing emergence of these multi-resistant organisms is the excessive application of antibiotics in medicine and farming, resulting in continuous exposure to antibiotics in these environments.



NIAID

Klebsiella is a genus of bacteria that easily aquires mutildrug resistance

The rapid emergence of multidrug resistant bacterial strains represents a serious ethical issue for the global community. Ineffective treatment does not just affect the patient, but has wider implications for the population. Worldwide, the evolution of drug resistance is the result of simultaneous over-consumption or incorrect use (such as a failure to finish the full course) of antibiotics by wealthy nations, and under-consumption by developing countries. In the latter, dangerous strains are rarely treated correctly due to the lack of medicines and treatment, and are therefore never fully eradicated. The same pathogenic strains can then be further selected for hyper-multidrug resistance in an environment like a patient's intestine, which is exposed to multiple antibiotics in a typical Western hospital. This interconnectivity means that health, especially in the context of MDR and infectious diseases, should be treated as a global public health concern, not just a national one. When microbes develop resistance in one patient because of over- or under-consumption of medication, this more dangerous malady poses an increased risk to others.

Compounding this, many international pharmaceutical companies have abandoned the development of new antibiotics. The rapid global spread of antibiotic resistance, which has significantly reduced the time span during which antibiotics are effective, together with the low prices of antibiotics have made return of investment problematic for many companies. A study by the Cambridge Judge Business School, examining the success drivers of the pharmaceutical industry, further confirmed that the antibiotic pipelines dried up some time ago. Even though new attempts to develop antibiotics and blocking agents of multidrug resistance have restarted recently, real progress is difficult due to a lack in our detailed understanding of the mechanisms by which drug resistance develops. In a development process aimed at launching sustainable drugs on the market, basic research on the evolution, spread and mechanisms of MDR is needed, more than ever, in order to overcome these roadblocks. This research can reveal surprising new insights that might become important therapeutically in the future.

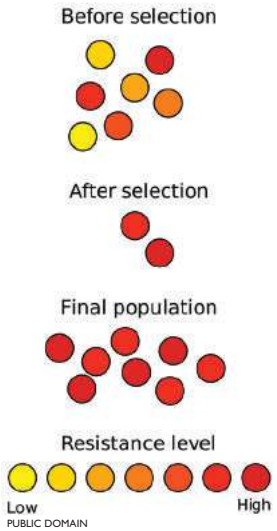
There are various mechanisms by which bacteria can survive under, and eventually adapt to, antibiotic exposure. Even non-mutated—or 'wild-type'—strains have a basic set of countermeasures to antibiotic stress. Drug efflux pumps are a good example. These are molecular structures (proteins) embedded in the plasma membrane of the cell, which can recognise and expel a vast range of

antibiotics from the cell before these drugs can do significant harm to the interior. Scientists in the van Veen group (Department of Pharmacology, University of Cambridge) believe that, in the first instance, these pumps allow wild-type strains to cope with increased amounts and complex cocktails of antibiotics. Studies have shown that the same strains suddenly become hypersensitive to drugs once the genes that encode these pumps are knocked-out. Other important mechanisms of antibiotic resistance act directly on the antibiotic through modification or degradation by enzymes.

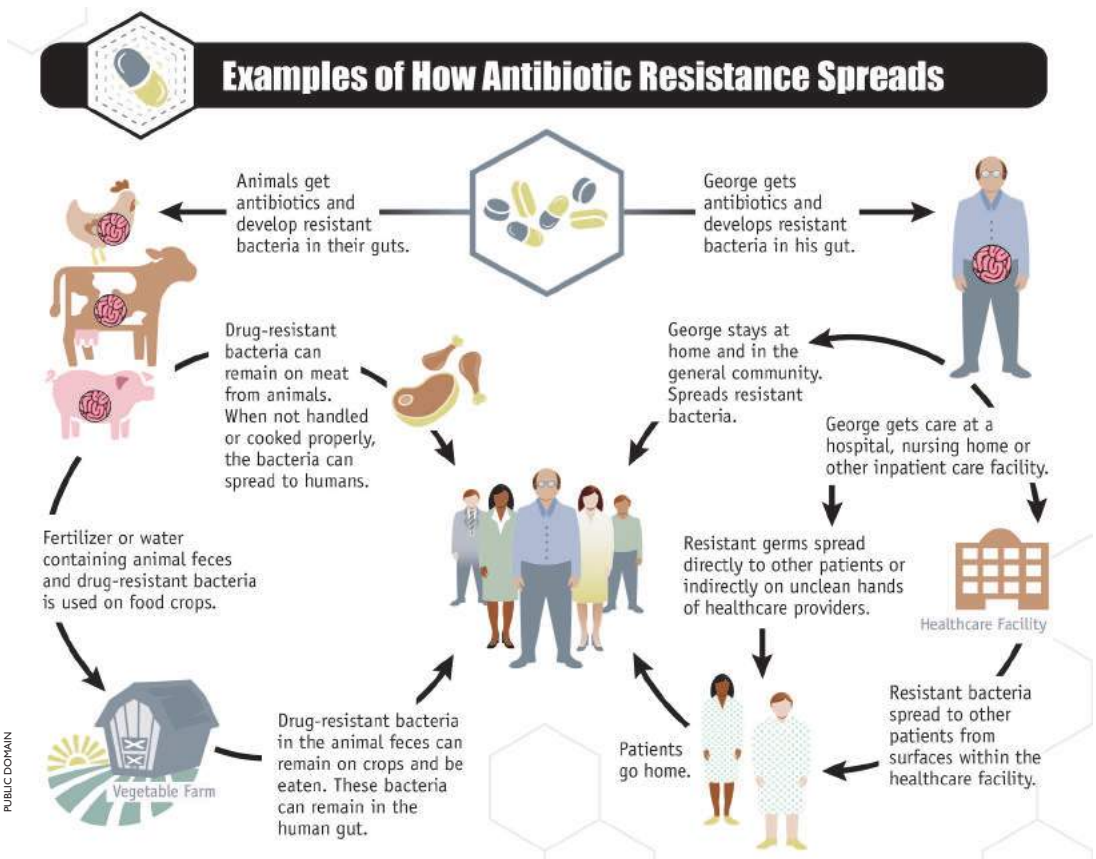
Existing mechanisms can be improved through genetic mutations; errors in DNA replication during cell division. Some of these errors can be beneficial for survival under certain conditions. For instance, a gene coding for an antibiotic-destroying enzyme could mutate in such a way that it can now recognise and degrade members of other chemical families. Alternatively, a mutation could cause a genetic variation of the drug target itself (for example, a protein or piece of nucleic acid to which the drug binds and therewith blocks this molecule's further actions and usage). These variations decrease the drug's capability to interact with these targets, thus reducing the effectiveness of the drug as an inhibitory agent. Drug resistance can also be acquired through the expression of an alternative target in the cell that interacts less well with the antibiotic.

Eventually, in the course of cell division, these resistance-associated genes are inherited by daughter cells and can also be forwarded to less resistant kinsmen, from either the same or other species, via genetic exchange. In the latter process, multidrug resistance-causing genes are copied onto a mobile DNA-carrier and via this, transferred by their donor to an acceptor bacterial cell. In other cases, bacterial viruses transmit resistance genes in the process of infections. As far as such interactions in bacterial communities are concerned, Lee and colleagues have shown that bacteria can be true altruists when it comes to dealing with antibiotic stress. They can secrete signalling molecules to help not-yet resistant cells deal with antibiotic toxicity, despite this having no obvious value for themselves.

Today, various research groups study different aspects of multidrug resistance worldwide; here in Cambridge, for example, the van Veen group are carrying out functional and structural studies of efflux pumps. We need a broad-stroke understanding of the mechanisms of MDR emergence and spread, both on a molecular level and in the context of global health care systems (detective, preventive, and corrective regulations and actions). Practitioners, policy makers and scientists are therefore invited to collaborate and engage in multidisciplinary, integrative research and decision-making, with the aim of combating one of the biggest threats that our society faces today.

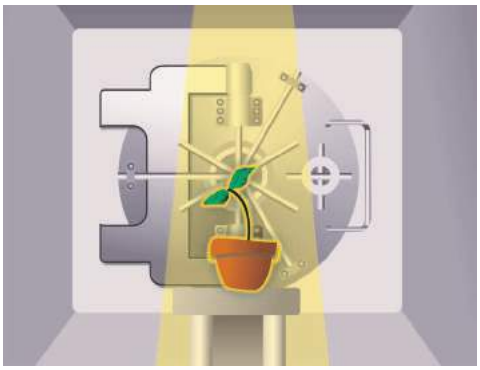


Development of drug resistance in a population of bacteria



Antibiotic resistance can spread in a number of ways, making the problem harder to manage

Arthur Neuberger is a graduate student at the Department of Pharmacology.



SARAH BINNEY

Variety: The Spice of Life

Janina Ander looks at the value of crop diversity for ensuring food security

Agriculture is at the intersection of two major challenges we face today: the fight against poverty—specifically undernourishment—and the adaptation to effects of climate change. 10.9 per cent of the world's population is undernourished and global temperatures are expected to rise significantly, leading to severe alterations in weather patterns. Luckily, there is one concept that could potentially open up excellent solutions for these issues: crop diversity.

Potato plants are often all clones - a lack of diversity that contributed to the Irish famine

Whilst we know of over 50,000 edible plant species, only 3 crops contribute to 60 per cent of our daily energy intake. Up until the first third of the 20th century, hundreds of distinct varieties of all these crops were farmed. However, many of these crops have been lost nowadays; between 1903 and 1983, 93 per cent of commercial seed varieties in the USA went extinct. What led to this depletion of crop diversity?

During the middle of the 20th century, the advent of the Green Revolution changed farming drastically. Beginning in the 1940s, dedicated breeding centres all over the world made systematic efforts to create high-yield varieties of crops. The new varieties, along with the growing use of herbicides, pesticides and fertilisers, as well as automation of agricultural practices, vastly increased the amount of grain harvested. By 1965, 95 per cent of corn grown in the USA was composed of new varieties, whilst in India, over three quarters of wheat acreage farmed in 2012 was high-yield. This sea of radical change in many countries resulted in a boost in global grain production. In fact, between 1950 and 1981, global per hectare crop yield grew massively, by more than 100 per cent.

On the surface, this seemed to be a positive trend and was likely the answer to an increasing demand in food supply for a steadily growing global population. Unfortunately, the yield per hectare plateaued, and no increase has been observed since 1985. Additionally, there were some negative outcomes of the Green Revolution. Many of the newly established varieties taking over were hybrids, i.e. the offspring of two very genetically diverse varieties. Whilst hybrid crops are often superior to either of their parents in producing grain, they themselves cannot produce seeds viable for replanting. This means farmers have to purchase hybrid seeds from agricultural corporations every year. Moreover, hybrids require increased irrigation and treatment with artificial fertilisers, as well as herbicides and pesticides. This, together with the mechanisation of agricultural production, resulted in pollution and higher emissions of greenhouse gases, as well as the erosion of arable soil. Additionally, whilst the hybrids yield large amounts of grain when raised under the right conditions, they are not bred to thrive in harsher climates or on infertile ground as found, for example, on the African continent. This difficulty contributes to the perpetuation of high rates of poverty and undernourishment in part of the African population.

Nevertheless, hybrid crops were widely embraced by farmers for economic reasons: farmers had to either adopt hybrids as their go-to crops or be out-competed by those farmers that did. In addition, farmers were incentivised to establish monocultures and eliminate crop rotation, since the cost of goods production decreases as the amount produced increases. These farming practices resulted in a vast decrease in genetic variation of crops. For example, corn in the US was grown in hundreds of varieties in 1930, but as early as 1969, 71 per cent of all corn farmed was from only six hybrids.

Why should we care about our crops' genetic diversity? Firstly, when one specific crop variety is very common in a region, diversity is lost and there is thus an increased risk of massive loss of grain due to plant diseases or parasites. Secondly, climate change will inevitably lead to changing and more variable weather. In all likelihood, crop yields will decrease if we do not have varieties that can thrive in these new circumstances.

Genetic engineering makes it much easier to integrate single genes into crops, for example to confer herbicide resistance. But many traits of plants do not correspond to one single gene that can be transferred between varieties by biotechnological means.

This is why today traditional breeding is still the prevalent means of improving crops. Breeding diverse crops that can be farmed in a variety of climate and soil conditions will help to maintain overall crop yields in the coming century, which will bring with it the effects of climate change. But this can only be achieved if genetically diverse crop varieties as well as their wild relatives are available. Therefore, conservation of genetic diversity is vital and multiple local and global programs have been installed to promote it.

Crop diversity protection programmes fall into two categories: in situ and ex situ. In situ programmes aim to maintain diversity on site, mainly by supporting small, mostly family-run farms that often do not produce much more grain than the families need for themselves. It is estimated that there are more than 500 million family farms worldwide and that they harbour 75 per cent of crop varieties. Organisations such as The Southeast Asia Regional Initiatives for Community Empowerment (SEARICE) or Agricultural Transition help to promote conservation agriculture. SEARICE do not push smallholders to adopt Green Revolution practices that are beneficial in the short-term but counterproductive to global crop diversity in the long-term. Instead, they support productive expansion of traditional farming methods. In this way, local communities are empowered to sustain themselves in an ecologically friendly manner. SEARICE also coordinates programmes that aim to actively increase rice and corn genetic diversity in the Philippines.

Ex situ crop diversity protection relies on seed banks. These are facilities such as the Svalbard Global Seed Vault (SGSV) on the Norwegian island of Spitsbergen about 1,300 kilometres from the North Pole, and the Millennium Bank at the Royal Botanical Gardens in Kew, UK, where vast amounts of seed samples can be sent for preservation. The Milllenium Bank alone currently contains 36,333 plant species and 2,115,847,290 individual seeds in storage, with these numbers still increasing.

Seed banks are chiefly used by scientists. For a long time their main purpose was to store seed samples of common crop varieties. In 2011, however, the Global Crop Diversity Trust started a project that aims to collect, maintain and analyse crop wild relatives of 29 crops for eventual interbreeding with established varieties.

The popular imagination is easily captured by a facility like the SGSV, a place in the middle of nowhere near the North Pole, where agricultural treasures might be saved even from an apocalyptic event. Whilst seed banks, especially those employing permafrost storage, do aim to preserve samples indefinitely, the fact remains that permanent storage cannot be accomplished: periodically, seeds have to be resown and new samples collected. Many funds are invested in the maintenance of seeds and also in the banks themselves. For example, the Global Crop Diversity Trust plans to raise $850 million between 2014 and 2024 for its ex situ projects.

Whilst seed banks are very useful resources for research, protecting genetic diversity of crops in situ directly benefits farm smallholders. If implemented widely and systematically, these in situ efforts could help to diminish undernourishment and poverty. This is clearly evidenced by multiple reports of the United Nations.

Sadly, their findings are not reflected in international assistance for developing countries. In the early 1980s, 20 per cent of Official Development Assistance was spent on agriculture, but by 2007 this was only 3 per cent. As the threat of climate change looms ever larger, we should hope that policy makers mandate changes that will preserve crop diversity as well as benefit the poorest among us. β

Janina Ander is a fourth year PhD student in Developmental Biology.

Wheat occupies 17% of all cultivated land in the world


CLAUDIA FLANDOLI

Overherd Immunity

Caitlin Stewart discusses the importance of vaccination and the dangers of the anti-vaccination movement

Vaccination has been all over the news in recent years, as deadly, vaccine-preventable diseases are returning and infecting the population worldwide. One of these diseases, measles, was declared eradicated in the USA in the year 2000, but has since made a resurgence; with a 3-fold increase in cases between 2013 and 2014, according to the CDC, and an additional outbreak reported earlier this year at Disneyland in California. Measles, caused by *Morbillivirus*, is spread by coughing or sneezing, and is highly contagious. Infection causes a high fever and a distinctive rash that covers the whole body. It is considered as one of the most deadly childhood fever illnesses, with children being at high risk of complications; including ear infections, seizures and pneumonia. An estimated one in 1000 childhood cases of measles even results in death.

The USA isn't alone in this phenomenon; an outbreak of pertussis, also known as whooping cough, occurred in the UK in 2012, with almost 10,000 cases recorded by Public Health England—that's 10 times the average number of cases and the largest outbreak in the UK for 20 years! Cambridge was especially hit hard, experiencing 20 times the average number of cases. Pertussis is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. Infection results in uncontrollable, violent coughing, making it difficult for suffers to breathe. After fits of coughs, sufferers quickly take deep breaths that result in the characteristic 'whooping' sound the disease is named after. Although similar to measles, it is more serious and deadlier in children, especially in babies less than a year old. In the UK, 14 babies less than three months old died during the 2012 outbreak.

Both measles and pertussis are vaccine-preventable diseases. John F. Enders developed the first vaccine to measles in 1963, and an improved vaccine with reduced side effects was introduced five years later. The pertussis vaccine was introduced much earlier, in the 1940s. Vaccination against both has been credited for effectively eradicating these diseases in the USA and other developed countries. However, vaccines are not effective in 100 per cent of individuals as certain people, such as those with immunodeficiency or allergies to the vaccine contents, cannot be immunised. These people rely on herd immunity—if the majority of the population are immune the disease cannot effectively spread and infect those who are non-immune.

Interestingly, the increase in these diseases is not due to ineffectiveness of the vaccines or adaption by the pathogens, but by individuals choosing not to vaccinate themselves or their children. As a result, not enough people are being vaccinated against these diseases to maintain herd immunity. The anti-vaccination crowd, or 'anti-vaxxers' as they are known, typically believe vaccinating will cause more harm than good. They spread information about the risks vaccines and their side effects pose to children—information which is sometimes incorrect or even fraudulent. This belief was started largely by a paper, published in 1998 in the Lancet by Andrew Wakefield, claiming the measles vaccine results in autism spectrum disorders when given to children. After it was published, multiple papers published in the BMJ suggested that Wakefield had manipulated evidence and that the results were fraudulent. This resulted in the paper being retracted, but the damage had already been done and some still believe


CLAUDIA FLANDOLI

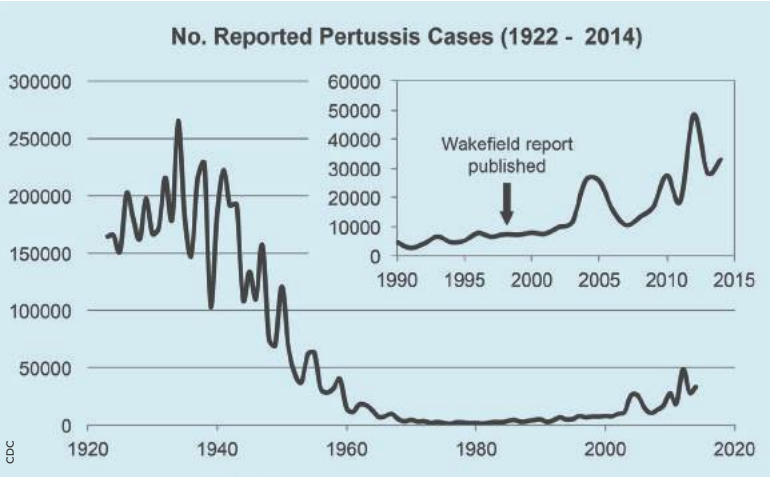
these findings. By 2006, cases of measles and mumps had increased, 13 and 37 times respectively, compared to their 1998 levels.

Vaccination does have side effects, although these are usually mild and can include fever, redness or soreness around the injection site. Serious side effects reported for the measles vaccine such as long-term seizures, coma or permanent brain damage are incredibly rare (<1 in a million doses); so rare that they cannot necessarily be attributed to the vaccine at all. These serious side effects are often portrayed as being common by anti-vaxxers and cited as reasons to avoid vaccination entirely. Another reason against vaccination is the belief that the current schedule includes too many vaccines at once or too close together, overloading a child's immune system, resulting in brain damage and/or autism spectrum disorders. There is no scientific evidence supporting this. The unfortunate reality is that the measles vaccine is administered during a baby's first year, a time when the emergence of autism spectrum symptoms, such as the regression of communication and other skills, quickly follows. This can lead some parents to mistake correlation for causation.

These parents fear harm coming to their children, and the availability of incorrect information about the risks of vaccines online has led them to believe the dangers of vaccination outweigh the benefits. It has been suggested that many anti-vaxxers have grown up without experiencing the symptoms and consequences of vaccine-preventable diseases, and do not realise the risks these diseases pose, or the reality of the danger they are putting their children in.

Many methods to change the minds of anti-vaxxers have been tried—most frequently the scientific evidence of their safety and absence of a link to autism is explained. Unfortunately this has been shown in previous studies to be ineffective and can even backfire—where some vaccine sceptics formed even stronger negative opinions about vaccination when this information was given to them and their views were challenged.

A more recent study, looking at changing the attitudes of anti-vaxxers was published by Horne et al. and showed encouraging results. However rather than trying to convince vaccine sceptics of no link between vaccination and autism, they tried to convince them of the negative effects of having no vaccination; i.e. that being unvaccinated leads to a high probability of catching a preventable disease and that the consequences of these illnesses are severe. 315 participants were first assessed for their attitudes towards vaccination, then randomly assigned one of three types of reading material ("Disease Risk", "Autism Correction" and "Control" scientific literature), before finally being assessed again. Those assigned reading on Disease Risk received a paragraph



from a mother describing her child contracting measles, a picture of children with measles, mumps, and rubella, and three short warnings about how important it is for people to vaccinate their children. Those reading about Autism Correction received materials from the CDC website summarising research that shows vaccines do not increase the risk of autism in children. Control scientific literature was on topics unrelated to vaccination. There was a slight increase in support of vaccination after participants read the Autism Correction literature compared to the control. However, this was not statistically significant. On the contrary, reading about Disease Risk increased support for vaccination in six times as many people as in the control group, a highly statistically significant result. Showing them the risks posed by the disease may have caused them to re-evaluate their attitudes towards vaccination to see that the benefits outweigh the risks. This is an important step forward in ensuring anti-vaxxers and the public are properly informed about the risks of remaining unvaccinated.

This type of shock tactic is similar to the anti-smoking campaigns showing diseased lung tissue and has been successful in other areas, suggesting it could be effective in changing anti-vaccination attitudes on a larger scale. To implement this, the authors suggest making this information more readily accessible on the internet and as easy to find as anti-vaccination information is currently, which can be found within a few clicks. Additionally, including this information in baby visits with parents would provide excellent opportunities to ensure higher vaccination rates in the future.

As somebody who fell victim to whooping cough during the last outbreak, desp ite being vaccinated, stemming the tide of these diseases from spreading and ensuring everyone is protected is a welcome prospect.

Caitlin Stewart is a final year PhD student at the Wellcome Trust Sanger Institute.


CLAUDIANA GOIS

Is the Way to our Hearts Through our Stomachs?

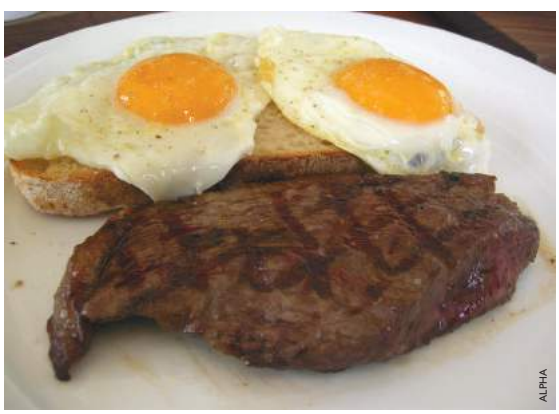
Kimberley Wiggins explores the role of gut microbes in cardiovascular disease

With the increasing popularity of 'superfoods', health kicks, and slogans like "tummy loving care" our generation have become much more aware of the bacteria in our guts than ever before. However, it seems that our intestinal inhabitants influence a lot more than just our digestive system. The first bacteria colonise our gut before we are born, entering our body via the placenta. By adulthood it is estimated that there are 100 trillion bacteria per gram of our intestinal tract - our body actually contains many more microbial cells than human ones. Our relationship with these microorganisms is reciprocal – we give them somewhere to live and in return they help us to process food, influence our metabolism and contribute to our immune system. In fact, scientists are beginning to consider our microbiota as an unconventional organ that releases biologically active molecules that are carried in the bloodstream, similarly to hormones, to other sites around the body.

Most of us know that a poor diet can lead to cardiovascular problems. At the top of the proverbial hit list are excess saturated fats and sugary carbohydrates. Less obvious culprits are certain nutrients that we might assume can do us no harm. Some foods including eggs, milk and red meats contain nutrients such as choline and carnitine that have a biochemical structure with a trimethylamine (TMA) group. This group is processed by the gut bacteria to generate a gaseous version of TMA, which can enter the bloodstream and reach the liver where it is oxidised to trimethylamine N-oxide (TMA-NO). Elevated circulating levels of TMA-NO are associated with increased cardiovascular disease. The essential role of microbiota in this process has been confirmed by feeding choline to mice with and without gut bacteria. Choline only triggered the development of disease if the microbes were present, and treating the bacteria-containing mice with antibiotics (thereby killing the gut bacteria) prevented disease development. But how?

To understand the mechanism, it is first important to appreciate exactly what vascular disease entails. Atherosclerosis is a chronic inflammatory condition of the artery wall that precedes cardiovascular events including heart attacks and strokes. At certain locations within arteries, such as areas with disturbed blood flow, the endothelial cells lining the inside of the vessel, become damaged and leaky. This allows lipids to enter the vessel wall, which results in recruitment of immune cells to the area. These immune cells take up the fats but are unable to process them, becoming inactive 'foam cells' that eventually die. This affected area of the vessel is known as a plaque. The contents of the plaque are contained by structural proteins like collagen, which are produced by smooth muscle cells to form a 'cap'. However, as the contents of the plaque become increasingly inflammatory and toxic, the smooth muscle cells die and the cap weakens. Eventually the cap ruptures and the contact between the plaque contents and the blood activates the coagulation system, a blood clot forms, the vessel is blocked, and the patient experiences a heart attack or stroke depending on where in the body the event occurred.

Research has shown that feeding mice TMA led to an upregulation of so-called 'scavenger' receptors, which mediate uptake of lipids, on the surface


ALPHA

Foods high in choline and carnatine can increase risk of cardiovascular disease

of plaque immune cells. This in turn resulted in increased foam cell formation. It also triggered a reduction in a process called reverse cholesterol transport, which is the body's way of getting cholesterol out of the tissue and back into the liver where it can be excreted. There is also evidence that TMA-NO may worsen glucose intolerance and interfere with insulin signalling, potentially contributing to the development of diabetes.

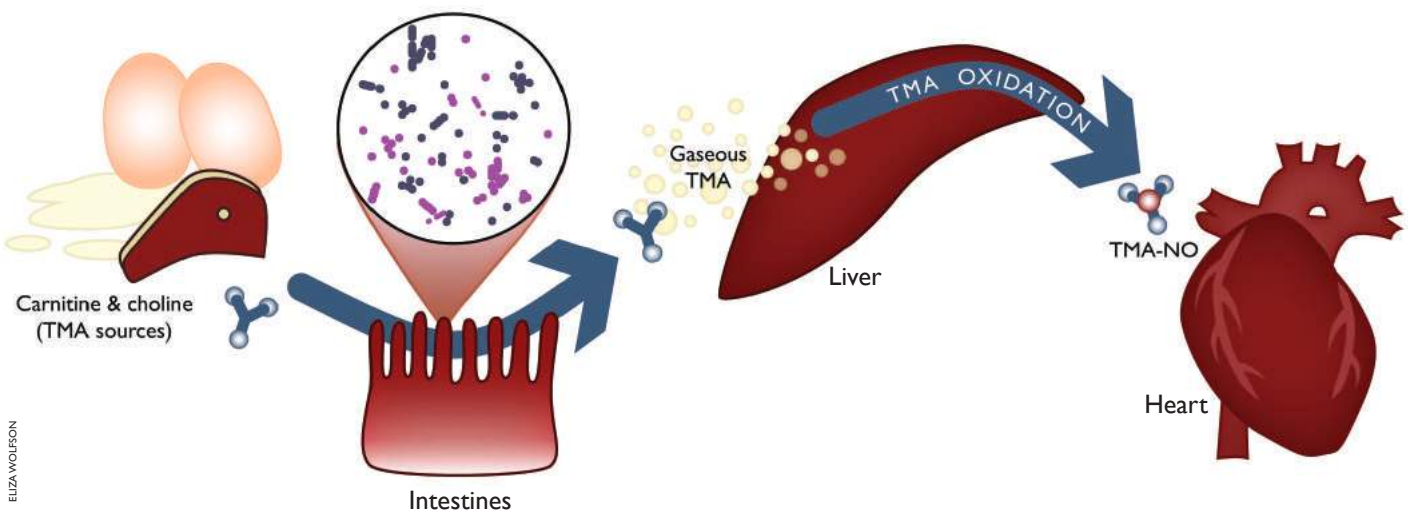
So, what does this mean for the treatment of heart disease? How could we interfere with the TMA-NO pathway to prevent its detrimental effects on atherosclerosis development? Perhaps the most obvious solution is to change our diets. Red meat contains high levels of carnitine – so should we become vegetarian? Research shows that vegetarians and vegans have a different profile of gut bacteria compared to omnivores and are less able to produce TMA-NO from carnitine. However, the other major TMA-including nutrient, choline, is also found in egg yolk, liver, fish, some dairy products, and certain nuts. That's a lot to give up! To make things more complicated, choline is also an essential nutrient – a deficiency is associated with neurological problems. Furthermore, bile contains high levels of choline, and so our stomachs are exposed to it regardless of whether we ingest this compound or not. It seems that nutritional modification could help, but this wouldn't totally solve the TMA-NO issue.

Maybe we could target the microbes themselves? If we identify exactly what enzymes in the bacteria process the TMA, we could block them. The issue with this is the huge diversity of microbes found in our intestine – one drug is unlikely to hit them all. Another option is to modify this diversity by introducing certain microbes through taking pro-biotics, or influencing the microbes already present using pre-biotics.

Finally, we could block the pathway at the level of TMA-NO production. After all, this is the compound that is harmful to our health. To do this we would need to target the enzyme within the liver that oxidises TMA, which researchers believe is Flavin containing monooxygenase 3 (FMO3). People who have a genetic defect in FMO3 have elevated TMA levels, presumably because they cannot convert it to TMA-NO, and this causes them to have particularly bad body odour (the condition is known as fish-odour syndrome). The current issue with targeting FMO3 therapeutically is that we do not fully understand the other functions it may have – if we inhibit it we may have detrimental off-target effects elsewhere.

Like most organs in our body, the gut microbiota is not perfect. It comes with design flaws that can predispose us to disease. However, unlike most organs in our body, it is directly druggable, and hence relatively easy to target. Every drug you take comes with a leaflet with a list of possible side-effects, but if we generate compounds that target only bacterial genes or proteins we would avoid interfering with the human cells surrounding them. Although the development of drugs that modulate the TMA-NO pathway requires a deeper understanding of the molecular interactions involved, it represents a real candidate for future cardiovascular therapies. In the meantime we can help ourselves by eating those TMA-containing nutrients in moderation, pushing our palate towards the power of plants, and reducing other cardiovascular risk factors such as smoking and obesity.

Kimberley Wiggins is a PhD student in the Department of Medicine.



Conversion of trimethylamine (TMA) from meat and dairy products into TMA-NO which is associated with heart disease

ELIZA WOLFSON

A Fly in the Ointment

Ben Moore discusses how fruit flies are helping to unravel the mysteries of human disease

It's 1986, and cinema audiences are being treated to The Fly, a sci-fi thriller in which an eccentric scientist manages to mix up his genetic make-up with a common housefly following a teleportation experiment. Whilst the highly logical among us might scoff at the idea, flies are in fact not so different from humans, and scientists are using the fly to understand and develop treatments for complex diseases such as cancer and schizophrenia.

Drosophila melanogaster, the fruit fly, has been used as a model organism for over a century. Charles Woodworth's and Thomas Morgan's pioneering work in the early 20th century developed ideas about inheritance and set the foundations for the use of *Drosophila* as an organism to study cell biology.

Drosophila melanogaster, the fruit fly, has been used as a model organism for over a century

MASUR

Whilst the use of fruit flies to study diseases with well-defined genetic causes seems relatively simple, the use of flies to study both cancer and complex neurological disorders, with their multitude of forms and causes, is quite remarkable.

A number of qualities about the fruit fly make it a fantastic model organism. Firstly, their short lifecycle means that experiments can be carried out in a much shorter space of time than experiments performed with rodents. Secondly, flies are very unfussy, which means housing and breeding them is less expensive and more efficient.

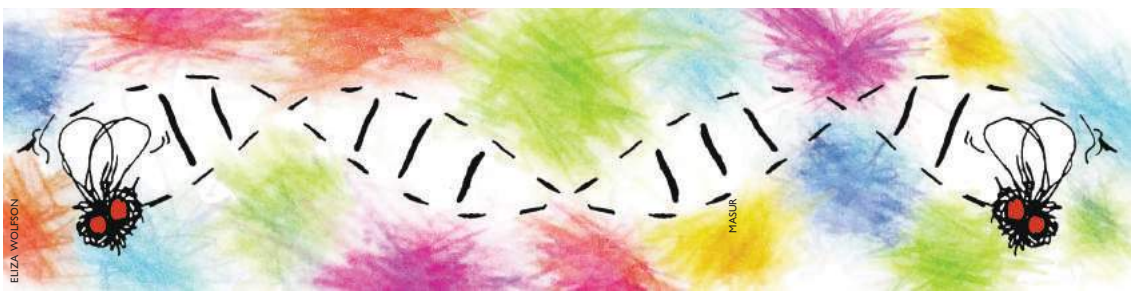
Also, flies have only 4 pairs of chromosomes (compared to 23 for humans!), which means that mapping genes is simple and over 50,000 fly stocks with mutations in specific genes have been generated and are accessible for the wider community. In fact, the Bloomington Drosophila Stock Centre at Indiana University has a dedicated list of fly stocks that model various human diseases, including Alzheimer's disease, Huntington's disease and a number of metabolic diseases, including diabetes.

Most importantly, though, evolutionary conservation means that the processes that dictate cell biology and the cellular signalling pathways that regulate them are often very similar between *Drosophila* and humans. Therefore, important conclusions from fly-based experiments can be extrapolated to humans.

There are a number of characteristics of cancer that make it so enigmatic to understand and treat. The first is that whilst 'cancer' is an umbrella term that describes a disease in which cells uncontrollably divide and invade surrounding tissue, these are really the only common features of all cancers. Cancer can form in any cell type, in young and old, and is caused by unrepaired damage to your DNA, leading to cells losing control of their in-built control systems. Your DNA endures a barrage of attacks from damage-inducing agents every day and most damage is normally faithfully repaired. However, cancer forms when a number of 'genetic lesions' go unrepaired in regions of the DNA that are important to regulating cell behaviour.

There are a number of cellular processes that are known to cause cancer when deregulated, and so evolutionary conservation between *Drosophila* and humans make fruit flies an excellent system for modelling the development of cancer. For instance, the growth of tumours can be modelled in the developing tissues of fly larvae. The group of Josef

Drosophila: Finding a solution for cancer therapy design?



ELIZA WOLFSON

MASUR

Penninger in the Peter MacCallum Cancer Centre in Melbourne, Australia, have performed a screen of thousands of genes to identify novel regulators of cell growth and invasion of cells in the eye and antenna. They recently identified a number of genes associated with cell organisation and orientation that promote cell growth and invasion when mutated.

When a patient is diagnosed with a particular type of cancer, the morphological features of the tumour and its constituent cells give no indication of the specific changes in their DNA that allowed them to develop cancer. Causative mutations that can be easily targeted are only described for a handful of cancers, but comparison of DNA from cancer cells to the DNA from non-tumour cells using DNA sequencing is starting to shed some light on specific DNA lesions that lead to cancer. However, much more work will need to be carried out to uncover how these specific mutations confer the properties of cancer cells, and how they could be targeted with therapeutics.

One of the main problems facing scientists tackling cancer is that tumours can arise from a combination of mutations, and individual tumours will have a particular 'signature' of genetic mutations that can lead to its formation. What this means is that the cancer of each patient is effectively unique. Unfortunately, this means that a cancer therapy that works well for one patient may not be as effective for another. Hence, for therapies to be effective treatment will need to be personalised.

And this is where the benefits of the fruit fly as a model organism have allowed it to be used to develop personalised cancer therapeutics. Ross Cagan and his teamat the Centre for Personalised Cancer Therapeutics in Mount Sinai hospital, New York, have developed a highly efficient system in which tumours are analysed for their mutational signature and a fly stock containing these mutations is rapidly produced and grown. These fly 'avatars' are then fed on food laced with various concentrations and combinations of a number of known chemotherapeutic drugs. Survival of the flies under different treatment regimes indicates the most effective treatment method, and this information is fed back to clinicians to advise their treatment protocol. The flies are so personalised that diabetic patients have a fly stock fed on a high sugar diet!

The realisation that flies, and perhaps other model organisms, can help develop personalised cancer therapeutics truly represents a new dawn in cancer treatment.

Finally, and more impressively, the fruit fly is providing important inroads in the study of complex neuropsychiatric disorders, such as schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD) and autism. The social behaviours of fruit flies such as their sleep/wake cycle, mating, learning and memory, aggression and sensory perception are being characterised in great detail. The realisation that despite the considerable differences in brain size and complexity, disruption of specific genes rewires these kinds of social behaviours in flies and parallels the symptoms of complex neuropsychiatric disorders in humans has opened a whole field of research using *Drosophila*.

This is exemplified by Fragile X Syndrome (FXS). FXS is characterised by mental retardation, hyperactivity, attention deficit and sleep disorders. It is now known that FXS is caused by a mutation in the FMR gene. Surprisingly, FMR mutant flies have similar behavioural impairments as FXS humans. For example, they are unable to maintain a normal circadian rhythm in constant darkness, and have impaired memory function. For FXS, testing the standard *Drosophila* behaviours in FMR mutant flies has provided a link between the molecular cause and physical manifestations of the disease. It has also opened doors in terms of testing viabilities of different therapeutic interventions. It is still not entirely clear to what extent social behavioural defects in flies are comparable to social problems in humans, but exploration of this is underway.

Rather than being quite a simple model organism, *Drosophila* possesses the qualities that make them useful to understand complex diseases.From simply understanding cell function and processes using an ever-increasing array of genetic manipulations, to attempting to pick apart the complex cause-and-effect relationships in neuropsychiatric disorders, the future in *Drosophila* research seems bright.

Drosophila is providing important inroads in the study of complex neuropsychiatric disorders

Ben Moore is a 4th year PhD student at the MRC Laboratory of Molecular Biology.

Malaria: The Path to Eradication

Malaria is a mosquito-borne infectious disease caused by the *Plasmodium* parasite

BlueSci looks at one of the globe's biggest killers and strategies for its eradication

Malaria is a disease as old as humanity - its history has been entwined with the history of civilisation. Some of the earliest known cases are from ancient times, confirmed by DNA evidence from Egyptian mummies. The recurring fevers typical of the disease were also described in ancient Greece by the doctor-philosopher Hippocrates. For centuries malaria remained endemic across Europe, from Greece and Italy all the way to the fens in South-Eastern England. Only in the early 20th century, with concerted eradication efforts, did its range change dramatically. Malaria still kills—annually there are an estimated 200 million cases and 500,000 deaths worldwide—but it is now classed as a tropical disease. 90 per cent of all deaths currently occur in Africa, and it is overwhelmingly a disease of poverty. The 20th and 21st centuries have seen great advances in malaria prevention and treatment, but controlling this disease has never been simple, and whether it will ever be eradicated remains to be seen.

Today we know that malaria is caused by a single-celled parasite, *Plasmodium*, and is transmitted by mosquitoes. *Plasmodium* parasites first enter the bloodstream when mosquitoes feed, and are then transported to the liver. Here they develop and multiply before re-entering the bloodstream and invading red blood cells, where they multiply again. Infected blood cells fill up with parasites and eventually rupture, which causes the characteristic 'paroxysm', a combination of fever and chills recurring every few days. This is so typical of the disease that most historical references to 'intermittent fevers' probably refer to malaria. The real danger, however, is not in the fever but the accompanying complications; these can range from respiratory distress to cerebral malaria, the latter causing life-threatening swelling of the brain.

It doesn't just end with fevers: malaria can also affect our response to other infections. The risk of malarial infection—and severe complications—increases with HIV infection, which given the large geographical overlap between these two diseases leads to an even greater disease burden. From the 1920s to the 1940s, before the advent of antibiotics, the malaria parasite was even used to cure syphilis: the fevers caused by the infection killed the heat-sensitive syphilis bacterium, whilst the parasite load was controlled with antimalarial drugs. Although the treatment had a 15 per cent mortality rate, this was far preferable to the absolute lethality of syphilis! Malaria has even shaped the human genetic landscape, the best-known example being sickle-cell anaemia. People with only one copy of the sickle-cell genetic variant have greater resistance to malaria, which is a major reason why sickle-cell anaemia persists today.

The malarial parasites were discovered in 1880 when a French doctor, Alphonse Laveran, observed them in the blood of malaria patients. In 1897 a British Army surgeon in India, Ronald Ross, demonstrated that mosquitoes could transmit avian malaria and one year later a team of Italian scientists showed that *Anopheles* mosquitoes were responsible for spreading malaria in humans. Both Laveran and Ross won the Nobel Prize for their work on malaria in 1907 and 1902 respectively, but it was not until 1942 that malaria parasites were shown to develop in the liver before entering the bloodstream. The final life cycle stage, a period of dormancy in the liver, was not demonstrated until even later in 1982!

For centuries beforehand the cause of malaria was a mystery. The name 'malaria' itself comes from the Italian phrase for 'bad air', because the stagnant air from swamps and marshes was thought to cause the disease. This was one reason why the inhabitants of Rome over the ages left the city for the summer and retreated to the hills; the nearby Pontine marshes were a hotbed of malaria until the mid-20th century. Since mosquitoes thrive in the stagnant water of marshland, this tactic worked, but was sometimes mistakenly taken as proof of the 'bad air' hypothesis.

Long before the cause of malaria was understood though, there were attempts at malaria control. The first method was broadly environmental. Throughout history, humans have attempted to drain swamps: the ancient Romans managed to partially drain the Pontine marshes, and the draining of the English fens in the 18th and 19th centuries largely put a stop to the 'Essex ague', a fever that was almost certainly malaria.

Efforts to eradicate malaria using DTT was largely successful in some parts of the world

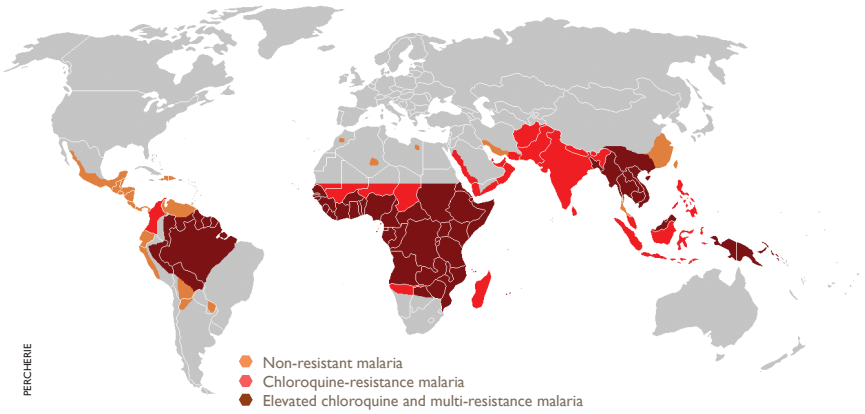
USCDCP

Even these measures only became truly effective when combined with knowledge of *Plasmodium's* life cycle and the invention of insecticides that directly targeted the mosquito vector. The USA's National Malaria Eradication Programme (from 1947 to 1952), for example, relied on DDT. While spraying DDT was subsequently banned in Asia and Africa, insecticides are still important today – usually to treat mosquito nets for household use.

The other way to control malaria is, of course, through antimalarial drugs that act against the parasite itself. Quinine is the original and most famous of these, but much like the draining of marshland, quinine was in use for centuries before Laveran saw *Plasmodium* down his microscope. Quinine is a compound present in the bark of the tree *Cinchona calisaya*, a native of South America related to coffee. The story of quinine in Europe began in Rome, when 10 cardinals and many more of their retinue died of malaria during the 1623 election of the Pope. Eight years later, *Cinchona* bark arrived in Europe for the first time, sent by a Jesuit apothecary working in Peru in response to the Vatican's demand for a cure.

However, *Cinchona* bark remained unpopular in Protestant England for many years thanks to its Catholic associations. During Britain's colonialist expansion though, *Cinchona's* status inevitably changed from 'Catholic poison' to essential medicine. By 1820, tonic water, a bitter mixture of cinchona extract and water, was used to prevent malaria in the British Raj. Adding gin and sugar was one way to make tonic water palatable; this habit persists in the modern gin and tonic, though it contains far less quinine than the original. The isolation and study of quinine also opened the way for the synthesis and discovery of many other antimalarial compounds, which are now an integral part of the current chapter of malaria's story.

Quinine and other alkaloids, such as cinchonine and cinchonidine, work through inhibiting the processing of haemoglobin, consumed by *Plasmodium* during the blood stage of infection. Normally *Plasmodium* store haem (a product of haemoglobin digestion) within their food vacuoles in an inactive form known as haemozoin. Inhibition of this process results in toxic accumulation of haem and death of the parasite. In spite of the apparent success of this treatment, quinine is very toxic, even in low quantities. Overdose can result in multiple unpleasant symptoms, known collectively as 'cinchonism', which includes impaired hearing, dizziness, diminished visual activity and even renal failure. In fact, quinine is no longer recommended by Food and Drug Administration, although it is on rare occasions still used for treatment of the most dangerous malaria infections.



Global distribution of malaria and resistance to current drugs

Instead, until recently, one of the most widely used anti-malarials was chloroquine. Its mechanism of action is similar to quinine, but is much less toxic to the patient. Being safe, cheap and effective, chloroquine helped spur on the malaria eradication efforts in the 1950s. Unfortunately, this therapeutic efficacy was halted with the emergence of drug resistance, something which plagues malaria treatment to this day. Resistance to chloroquine led to a resurgence of the disease and resistant strains can now be found world-wide in most malaria-affected areas. This resistance commonly stems from a mutation in the transporter PfCRT, allowing it to transport the drug away from its target.

With the rise in chloroquine resistance, new therapies were sought and a number of drugs have been developed during the last century, with various inhibitory mechanisms. One in particular has stood out: artemisinin. In fact, in 2015 the medical community commemorated its discoverer, Tu Youyou, by awarding her the Nobel Prize in Medicine. Using the knowledge of her ancestors, Tu screened 2,000 Chinese herbal remedies to find a drug with antimalarial activity. Her dedication was rewarded in 1972 when chemically pure artemisinin was extracted from the wormwood plant *Artemisia annua*. The discovery of artemisinin revolutionised antimalarial treatment and helped to reduce mortality to 20 per cent in adults and 30 per cent in children. Artemisinin destroys malarial parasites at an early blood stage, although the exact mechanism of action is not yet known. Out of all drugs available on the market artemisinin exhibits the fastest action against the progressing disease and artemisinin-based therapy has significantly alleviated the incidence of malaria.

The current gold standard for treating uncomplicated malaria is artemisinin-based combined therapy (ACT); a fixed dose combination of an artemisinin derivative and partner drug. However, like other malarial drugs, resistant strains have once again emerged and threaten the present malaria eradication effort. With resistance to artemisinin and its partner drugs being routinely identified in South-East Asia, new therapies are again being pursued. This includes the development of drugs targeting the blood stage, similar to most of the current drugs on the market, in addition to drugs targeting the liver and transmission stages of malaria infection. Drug development against the latter two stages have been hampered in the past due to lack of culture techniques and good in vivo models, however, they have the potential to stop malaria in its tracks. These drugs aim not only to treat the infection, but to stop people from getting malaria in the first place, and halting it from spreading.

One drug in particular has made the news recently, called DDD107498. Developed at Dundee University, it is about to enter the first phase of clinical trials. Unlike ACT, which requires two doses daily for three days, only a single dose is needed. This would decrease the risk of sub-optimal dosing due to non-compliance of the patient, a major factor in the spread of drug resistance. It is also affordable, likely to sell for less than a dollar per dose, and has the potential to stop people from getting symptomatic malaria to begin with. This is due to its ability to target both the blood and liver stage of infection through targeting a vital protein

Only the female mosquito feeds on blood as they need protein to help develop their eggs

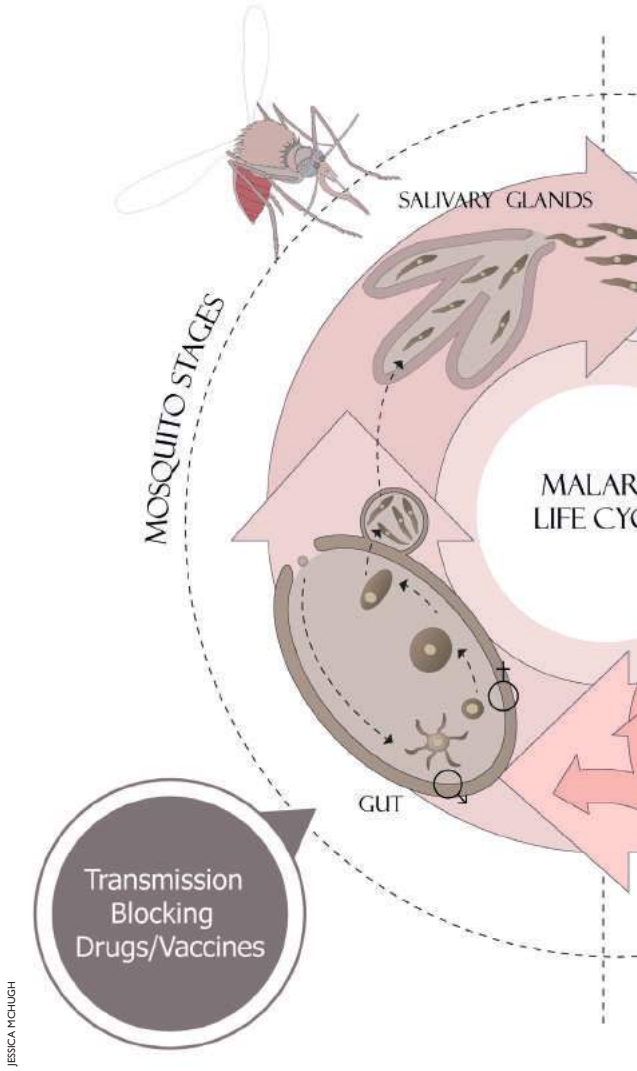
known as translation elongation factor 2, essential for protein synthesis in the parasite. By targeting this earlier stage, the infection is dealt with before any symptoms develop. Although this drug looks promising, there is still a long way to go before it can be used in patients.

The development of successful drugs has resulted in great progress in the battle against malaria, however, it does still remain an enormous global health burden. An arsenal of malaria control measures, including preventative action, drugs and ultimately a vaccine, will likely be needed if there is to be any hope of malaria eradication.

Complete eradication of a disease as global as malaria is a challenging prospect, made even more daunting by the fact that only one infectious disease affecting humans has ever been eradicated. The eradication of smallpox in 1980 was achieved largely through the widespread use of a vaccine. Scientists have spent many decades attempting to develop a malaria vaccine, however, they are facing significant challenges. The foremost of these is the parasites' complex life cycle. At each stage of its life cycle the parasite has a different morphology and will present different surface proteins to the immune system. This makes developing a vaccine that is effective against all the life cycle stages nearly impossible. So it is perhaps unsurprising that there is currently no malaria vaccine, or indeed any vaccine for a human parasitic disease.

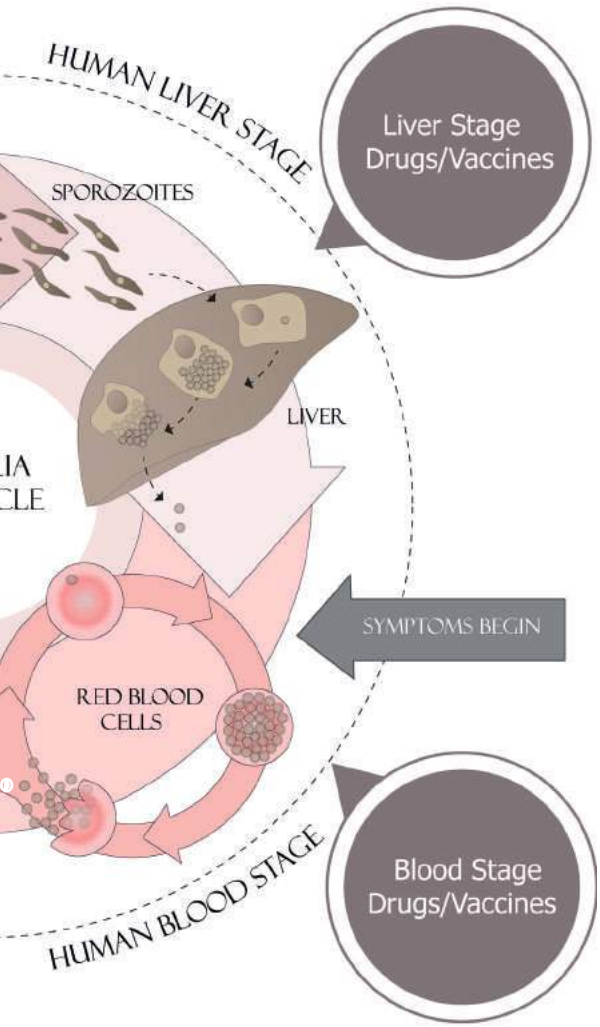
In spite of these challenges, many decades and billions of dollars have been spent researching possible vaccine candidates and conducting trials into what would make an effective vaccine. Most efforts have been focussed, and the greatest strides made, on *Plasmodium falciparum*, the parasite responsible for the most deadly form of malaria.

An intriguing possibility for a vector-borne disease such as malaria is a transmission-blocking vaccine. Perhaps counterintuitively, this type of vaccine doesn't actually prevent the person who has been vaccinated from getting malaria, but instead disrupts the life cycle of the parasite in the mosquito. Mosquitoes are thus unable to host the parasites and there is no way for malaria to spread between people. This makes it an attractive option for eliminating malaria from a region. The rationale behind transmission-blocking vaccines is to stimulate an antibody response to a form of the parasite taken up by the mosquito. This would theoretically block parasites from getting into or developing within the mosquito. A transmission-blocking vaccine based on Pfs25, a *P. falciparum* surface protein essential for parasite development inside the mosquito, is currently undergoing Phase I clinical trials in Mali. A vaccine such as this may one day help in stopping the spread of malaria – a step that will be critical if malaria is ever to be eradicated.



The lifecycle of *Plasmodium* consists of multiple stages in two vectors

Another attractive target for a malaria vaccine is the sporozoite. This is the parasitic stage at which the parasite first enters the human host following the bite of an infected mosquito. This stage is an attractive target because a vaccine that could prevent the relatively small number of sporozoites from getting to the liver and multiplying would effectively stop the infection in its tracks. It has long been known that immunisation with live, but inactivated, sporozoites is protective against malaria infection. This was first demonstrated in the 1970s when a study showed that 13 out of 14 volunteers bitten by about 1000 irradiated *P. falciparum* infected mosquitoes were protected from contracting malaria when later exposed. Sanaria, a US-based biotechnology company, was founded to develop this knowledge into a commercially viable and highly effective injectable malaria vaccine. Obviously, it is not practical to subject people to 1000 irradiated mosquito bites in order to vaccinate them, so Sanaria's first challenge



was to develop a way of directly injecting inactivated parasites. Sporozoites can be extracted from the salivary glands of irradiated mosquitoes by microdissection; they can then be purified and cryopreserved in liquid nitrogen, making their long term storage for a vaccine component a possibility.

In 2013, Sanaria showed that when six volunteers had more than 10,000 sporozoites injected directly into the vein over the course of five injections, they were all protected from contracting malaria from infected mosquitos. This pioneering experiment shows just how effective this technology could be in vaccinating people against malaria. However, it is not without problems. People were only protected if sporozoites were injected directly into the vein. This is a technically challenging route of administration that would require skilled staff, limiting the wide-spread use of this vaccine. Equally, dissection of mosquitoes to extract sporozoites is a labour-intensive process and one that requires highly skilled staff, again reducing the likelihood that this could be rolled out as a widely available and cost-effective vaccine. Nevertheless, Sanaria is currently conducting early stage clinical trials in the US and Africa. This vaccine has enormous potential but Sanaria has huge hurdles to overcome if it is ever to be widely used.

After decades of research a licenced malaria vaccine looks to be on the horizon. Just this year a Phase III clinical trial of a malaria vaccine known as Mosquirix was completed. Mosquirix, developed by British company GlaxoSmithKline, is the first malaria vaccine to advance this far in development. This vaccine also targets the early stage of a malaria infection. It triggers an immune response almost as soon as the parasite enters the human host and aims to disrupt sporozoites on the journey from the bite site to the liver. This immune response is to a protein called circumsporozoite protein (CSP), a major sporozoite surface protein and the main component of the vaccine. Sporozoite-targeted antibodies kill the sporozoites before they ever reach the liver and get a chance to multiply.

Mosquirix was trialled in more than 15,000 children in seven African countries over six years and was found to be successful at reducing cases of malaria. In children aged 5-17 months the number of cases of clinical malaria was reduced by 39 per cent. In areas where malaria transmission is high and clinical cases of malaria are common even a modest reduction in cases such as this will have the potential to save thousands of lives each year. The World Health Organisation (WHO) have recommended pilot implementation to see if it should be added to the toolbox of existing malaria control measures. It seems likely that before long there will be a malaria vaccine available.

With the development of Mosquirix the malaria vaccine research community has new goals to aspire to. Whilst Mosquirix is by no means a perfect vaccine, it is a starting point and may have huge benefits for the 3.2 billion people facing malaria every day.

In May 2015 the World Health Assembly set their strategy for malaria for the next 15 years, with the aim of a tenfold reduction in the incidence and deaths from malaria by 2030. Although there are many obstacles, such as resistance to current drugs and insecticides, new tools and approaches are expected to become available over the next decade, which will help this goal become a reality.

Kirsten Dundas is a fourth year PhD student at the Wellcome Trust Sanger Institute

Amelia Joy Thompson is a third year PhD student in the Department of Physiology, Development and Neuroscience

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ELIZA WOLFSON

Power to the People

Lachine Jardin discusses how the UK is navigating the road to decarbonisation

Electricity has become etched into the DNA of the developed world. In the UK, the electricity system has evolved over the last century to provide an economical and reliable supply of electricity. With increasing political pressure, this system is embarking on the road to decarbonisation. With many administrative and technological barriers to overcome, this journey will be long and difficult, and it is already off to a bad start.

The National Grid will be under immense strain this year as many power plants are retiring. Over the coming years, this situation is set to worsen. By 2023, most of the UK's 16 nuclear reactors, which generate about 18 per cent of the country's electricity, will be retired. In addition, according to plans drawn up by the Department of Energy and Climate Change for the UN climate change conference in Paris, coal-fired plants (which generated 29 per cent of UK electricity in 2014) will have been phased out by then.

In general, electricity is either generated for base or for peak load at each plant. Base load electricity is the minimum amount of electricity needed at any point. Peak electricity is everything above this, and needs to respond quickly to changes in demand; for example, to cover the kettle-induced energy surge brought on by the British public after any major TV event. To produce peak electricity, 'dispatchable' generation is used, as its output can be adjusted on demand. Between January 2010 and March 2016, the UK will have lost the capacity to generate 15.4GW via this dispatchable generation, making our electricity system much less resilient than it was only 5 years ago.

ELIZA WOLFSON

The energy trilemma sums up the difficulties currently facing energy production

It will require vast implementation of renewable, nuclear, and carbon capture and storage technologies to make up for this loss. To manage the transition, the UK government has effected a number of measures to improve the reliability and security of the electricity system and to stimulate investments. To meet EU air quality regulations, the lost capacity in the generation of electricity was expected to be replaced by gas-fired plants and large renewable projects. However, neither are being built quickly enough. It is predicted that the UK will not have enough generating capacity to cover peak demand next year. In other words, the UK is on the verge of an energy crisis!

In the midst of this, the future of the electricity system is being decided. Energy policy is attempting to balance the 'energy trilemma': security, affordability and decarbonisation. Historically, the focus has been on energy security and affordability, as they go hand in hand with economic development. More recently, decarbonisation has become essential to meet the legally binding emission reduction requirements set by the Climate Change Act 2008.

There are many different scenarios for a decarbonised future as no single energy supply solves the trilemma. Changes in the energy industry take many decades to become apparent and so it is unlikely that the availability of new forms of electricity generation will have a noticeable impact at any time soon. The UK is currently looking to use three ways to decarbonise electricity generation: renewables, nuclear, and carbon capture and storage (CCS).

If the UK is going to get serious about these changes, however, we need to be aware of their impact. David McKay, former Chief Scientific Adviser to the UK Department of Energy and Climate Change, has worked to provide clarity to this topic within both public and political debate. His book, *Sustainable Energy – without the hot air*, discusses various energy plans which add up to meet the current UK energy consumption. One point raised is that the power density is much less for renewable sources. For example, to generate all our energy needs with wind would require half of the UK to be covered in wind turbines - a renewable revolution would profoundly change our landscape!

Currently, both renewable and nuclear plants are also much less flexible than their fossil fuel equivalents. Renewables depend on the weather conditions, whilst nuclear generation cannot change rapidly in response to demand. Hence, on short timescales, the grid would be less responsive and thus less robust to quick changes in demand. Carbon capture and storage, which involves collecting 90 per cent of the carbon dioxide emissions released by fossil fuels and storing them underground, is also far from the easy option. Despite much of the technology already existing for use in enhanced gas extraction, it has not yet been tested on a large scale. In addition, trapping gas underground is not without its dangers: in 1986, a natural build-up of CO_2 beneath the volcanic Lake Nyos in Cameroon caused a cloud of lethal gas to escape, resulting in over 1,700 deaths. Thus precautions must be taken to ensure that the gas is stored safely, several kilometres below the surface.

Another issue with reneweable energy is capacity. To produce the same amount of electricity, intermittent renewables need to have a higher capacity than the equivalent fossil fuel plants. This is because renewables do not operate close to their maximum capacity. The National Grid will need to plan for this increase in capacity to deliver electricity effectively. To help encourage investment in reliable generating capacity, the government has stepped in and designed a Capacity Market, ensuring security of supply from existing energy plants from 2018. This market will help reduce the strain on the National Grid. In addition to this, the 'Contracts for Difference' arrangement aims to provide a stable revenue for plants providing low-carbon electricity supply. By providing this security, the government hopes to help developers secure investments, protecting customers from rising energy bills.

But what about the immediate future? There are ways to improve the current system. Electricity cannot be stored on a large scale, and hence supply must equal demand at all times. At the moment, this is achieved by demand governing supply. As intermittent renewables become increasingly prevalent, it is important to investigate into ways of managing demand as well. This would allow the National Grid to better control fluctuations and increase reliability. To a small extent, this is already being done.

BENKID77

The National Grid delivers electricity to homes across the UK

Extra tools have been implemented to increase the capacity margin; that is the average amount of extra electricity available compared to peak demand. These additional tools include the Supplemental Balancing Reserve (SBR) and Demand Side Balancing Reserve (DSBR), and so far have resulted in an increase from only 1.2 to 5.1 per cent, at a cost of 50p to the average consumer. The SBR consists of a network of backup generators, which can turn on to provide electricity if required. The DSBR is a primitive version of demand management. In addition, the National Grid can also turn off power supply to high demand users in cases of peak demand to prevent blackouts. With these measures, the National Grid can be confident that it can still operate effectively over the winter months but, if a large supply deficit does occur, customers may still be disconnected.

There is still a long way to go before the energy trilemma is solved and many hurdles lie in the way. In the face of many power plant closures, several measures have been put into place to help address issues with the transition. However, it is too little and too late? Only time will tell.

Lachine Jardin is a PhD student in the Department of Engineering.

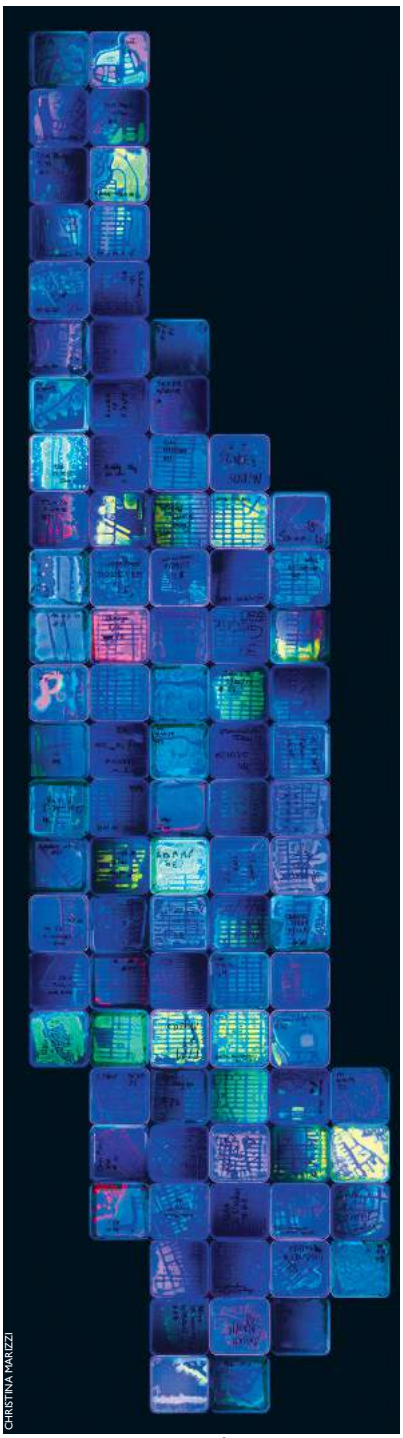
NBPTUUL/CC-BY3.0

Approximately 10% of the UK's energy is generated by wind farms such as this

Microbial Masterpieces


M PENIL & M BERKMEN

Zoe Carter explores the use of bacteria to create pieces of art


CHRISTINA MARIZZI

NYC Biome map - 2nd place in this year's ASM Agar Art competition

"One of my favourite things about great art is that it shows me the world in a way I've never seen it before," – a comment on the American Society for Microbiology Facebook page summing up the spirit of its recent competition: a unique agar art competition. Although bacteria may not be the most obvious choice for creating art, the collaboration between scientists and artists saw the emergence of some truly spectacular pieces.

One reason the American Society for Microbiology ran the competition was to help to overcome the public's negative perception of bacteria - a key criterion taken into account by the judges. Mehment Berkmen, a scientist at New England Biolabs who teamed up with artist Maria Penil to produce two winning entries, described the ability to change the public's view of microbes as "empowering" and highlighted that we often encounter microbes "in the context of sickness and disease", yet we rarely "mention how amazing they are".

Berkmen and Penil's winning petri dish, named *Neurons,* was created with bacteria that produce coloured pigments called carotenoids including the orange *Deinococcus* and yellow *Nesterenkonia* strains. These bacteria were painted onto agar and allowed to multiply for two days at 30°C. When the image was perfect, epoxy resins were used to stop new growth and preserve the artwork. The duo also won the people's choice award with their dish *Cell to Cell*, which aimed to "bring the communicative microscopic world to our macroscopic visual delight". Second prize was awarded to the *NYC Biome Map*, created by 50 citizen scientists at Genspace, the NYC community biolab. Harmless E. coli K12 bacteria that had been genetically engineered to produce green, red or yellow fluorescent proteins were grown on 94 square agar plates that, when arranged together, created a street plan of the Big Apple. Explaining what inspired this magnificent map masterpiece, project coordinator and lab educator Christine Marizzi wrote "NYC is a melting pot of cultures, both human and microbial. Collectively we shape NYC's microbiome by our lifestyle choices, and the unseen microbial world significantly impacts us."

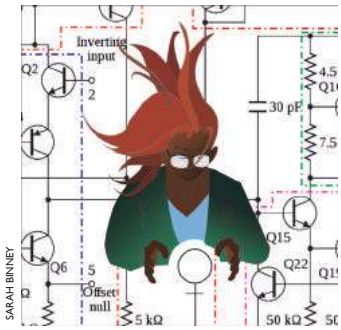
Not all the winning pieces were bacteria-based. Yeast was the star of the bronze medal plate, submitted by Maria Eugenia Inda from Argentina. The yeast strain *Saccharomyces cerevisiae* is used to make bread, wine and beer, but is also extensively used by scientists for genetic and molecular cell biology studies. For the competition, the signalling pathway within the yeast cells that controls the production of beta-carotene (the compound that makes carrots orange!) was engineered to create a colour palette of yellow through to red. These were ingeniously painted into a scene to represent the *Harvest Season.*

Many other imaginative pieces were submitted, including a bacterial replication of Van Gogh's *The Starry Night*, a piece named *Micro-Monet* and an Andy Warhol inspired petri dish collection. A plethora of colouring methods was employed, including a strain of bacteria (*Delftia acidovorans*), which 'makes its own art' by staining the agar through anthranilic acid secretion. For his entry *Flowering Sunshine*, Manal Hamed from Qatar included a pH indicator in the agar. The colour of this indicator changed as the E. coli grew, because the bacteria naturally ferment sugars present within the agar to produce acid, thereby creating the colour palette for his piece

Professor Dennis Bray, a researcher at the University of Cambridge and one of the competition judges, was "pleasantly surprised" by the 80 or so submissions, saying "Some were highly skilled and artistic, with beautiful forms and colours - quite remarkable considering their provenance. Evidently a great deal of expert knowledge was involved in creating the plates, as well as time and creative energy."

Beautiful bacteria represent the largest biomass on the planet and now, thanks to art, they are beginning to get the recognition they deserve. β

Zoe Carter is a second year Natural Sciences student.



Robogals

Laura Nunez-Mulder discusses an initiative inspiring girls to become engineers

The UK is facing a critical shortage of engineers. It also has the lowest proportion of women in engineering in Europe. Australian Marita Cheng, founder of Robogals, believes that the solution to both these problems lies in education, aimed at young girls. To raise a generation of diverse engineers, she is opposing the self-perpetuating stereotype of engineering as a career for male minds by inspiring girls to consider engineering.

Founded in 2008, Robogals—run purely by students—has spread rapidly from Australia to countries all around the world, including the UK. The idea is simple: to show girls in primary and secondary schools that engineering is more than "hard hats and engines" through hands-on activities, specifically problem-solving activities involving Lego robots.

It is easy to see how Robogals' workshops capture the creative imaginations of schoolchildren: they are dynamic, versatile and immensely fun. The Lego robots used can move, sense light, draw letters, follow a line, send text messages and talk. However, to realise the full potential of the robots, children must first get to grips with basic computer coding.

A typical session involves initially introducing a group of children to the robots and coding software. Then follows a series of challenges, beginning with a simple "make the robot move" and progressing from there. The workshop is rounded off with a talk from an engineer; perhaps someone who improves prosthetic limbs, or who is refining the most sensitive syringe.

Jenni Sider, a research associate of the Department of Engineering at Cambridge University, is the Schools Manager of the Cambridge chapter of Robogals. She got involved when the Cambridge chapter was established, two years ago, because she was frustrated by the lack of women in her department.

"Engineering has a bad rep. Many of the girls I meet have an impression that you have to like cars to be an engineer, but there's far more to it than that. Engineering is creative, it is broad, it is dynamic." Jenni was fortunate to have a father and an uncle in engineering who encouraged her and involved her in their work, but many girls never gain this kind of insight into the profession.

Robogals road show in action: learning to code robot instructions

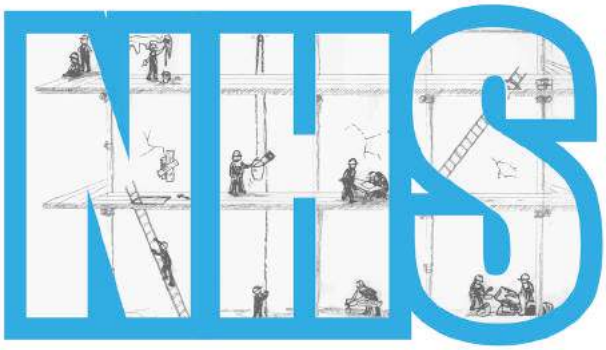
When Jenni became part of the Cambridge Robogals team, it consisted of three volunteers. Since then, they have received an incredible level of support, with sponsorship from large technical firms. They've been involved in collaborations with the Cambridge Science Centre, the Cambridge Science Festival and even the BBC, with 'Girls Can Code', which shows five girls starting coding from scratch and competing with their new abilities and aired on BBC3 last September.

An ordinary term with Robogals will typically see two or three half-day workshops. The coding skills can be picked up quickly, so new volunteers can join in straight away even without coding experience, and it is new volunteers that Robogals in Cambridge really needs. The end of this academic year will see the original core of volunteers leaving Cambridge; they do not want the potential for Robogals to dwindle away.

Jenni has seen for herself the powerful impact that Robogals has on the next generation. "At the start of a large-group workshop, the children often seem to be standoffish – especially the girls. But they transform in that instant that they first succeed in making a robot move. It's such a change. They see that they have the ability, the creativity for the task. And by the end, the children are asking engaged questions – like, 'How do I become this specific type of engineer?' That's how I know the true value of the work we do." β

Robots: not just for girls!

Laura Nunez-Mulder is a second year medical student at Emmanuel College.



ELIZA WOLFSON

The Contracts

Krishnaa Pandya discusses the impact of changes to the NHS contracts

Last October, 20,000 people gathered in London to protest against changes to the junior doctor contracts that are to be enforced in August this year. 'Junior doctor' is a misleading term applied to the majority of the doctors in a hospital, except for the most senior doctors, who are consultants. This altered contract has been made to match the government's 'seven-day' NHS system, however, it risks overworking junior doctors, to the point where they will be tired and stressed whilst treating patients. Overworked and underpaid young professionals, running on little sleep, creates a danger to patient safety. But that is not all that will change with this imposed contract.

The main change to the contract is the definition of working sociable hours. Currently, 7pm-7am weekdays and all-day weekends are classified as 'unsociable hours' and have a higher pay associated with working these hours. This provides a financial incentive to encourage junior doctors to work in departments such as A&E where there is a large amount of night or weekend work. With the new contract, working 'sociable hours' will be from 7am-10pm, Monday to Saturday, meaning those who used to work nights will now see their pay reduced as several hours have become 'sociable'. This does not necessarily mean doctors will be working more, but these new shift patterns will stretch the working day out, tiring doctors who will have to work until 10pm, and interrupting their work-life balance. This will make it difficult for those with commitments and families and increases the stress levels of junior doctors. By reducing the pay of junior doctors, whilst expecting them to work more nights and weekends, we place a growing burden on our junior doctors as demands on the NHS increase, possibly even jeopardising its future.

Pay scale is another large factor of this contract change, and will affect many areas of our healthcare system. Doctors have a hierarchy and banding system, with increased pay depending on band and place in the hierarchy. For example, a registrar (a doctor undergoing speciality training) is below a consultant in band, and will therefore have a lower pay, but a stage seven registrar will have a higher pay than a stage one. The new contract looks to change this. There will be less of a pay increase within each band, meaning that someone who has been at a particular stage for many years, and has a wealth of knowledge

UMAR HASSAN

There have been many protests by doctors against the changes to contracts

and experience, will be paid only minimally more than someone just entering that stage. Instead of pay increasing year on year, pay will increase depending on the amount of hours worked in the previous year. This change will be detrimental to doctors with families, and doctors who spend certain days researching medicine rather than practising clinical medicine. Pay will also affect doctors who wish to train in a different speciality, either as a change in job or to specialise in a particular niche in medicine. Currently, if a doctor wishes to re-train in a different speciality, their pay is safeguarded. With the new contract, their pay will fall to the starting salary of junior doctors, which is £22,000. This can be a large deficit, especially for those who are re-training in order to specialise into a niche field, for example a paediatric doctor re-training in audiology to become a paediatric audiologist. This loss in pay can have a huge effect on the doctor's psychological wellbeing, which may lead to mistakes being made in the management, diagnosis and treatment of the patient. As well as this, the incentive for doctors to retrain is decreased, and could result in a shortage of specialised doctors in these important niches.

The new contract will not just affect hospital staff, but also medical students and GPs. With the increase in tuition fees and poor starting salary, many medical students may seek alternative careers or even look abroad. Since the decision to force the contracts through, the General Medical Council has received more than 3000 requests from doctors for a certificate in order to work abroad. In order to become a GP, graduate medics must undertake their first two years as foundation-year doctors, followed by three years of specific GP training. During each year of this training, they receive a supplement to ensure their pay is comparable to those who train in hospitals. This supplement fluctuates around £15,000 each year, but will be scrapped under the new contract. This will reduce the financial incentive to become a GP, which may make the current GP shortage even more severe.

This long list of changes to junior doctors' contracts is founded on Health Secretary Jeremy Hunt's proposal for a 'consistent seven-day hospital service'. However the NHS is already a consistent seven-day 24 hour service. Junior doctors already work nights and weekends, and although consultants can opt out of non-emergency weekend work, they are almost always all on-call. Therefore, when an emergency does occur, consultants are within a 15 minute commute to the hospital and will come in any time of the day or night. The media and Health Secretary have claimed that patients are "15 per cent more likely to die if admitted on a Sunday compared to a Wednesday". In truth, this statistic is not as straightforward as it is portrayed. The study from which this statistic was taken, looked at 14 million admissions to NHS hospitals during 2009-2010. Of these, 300,000 patients passed away within 30 days of admission, and it was found that patients had a 15 per cent higher risk of dying within this 30 day period if admitted on a Sunday compared to a Wednesday. This information does not prove there is a higher mortality risk due to the way the hospitals are operated at the weekends, and fails to account for the possibility that patients admitted on the weekend may be in more critical conditions than those admitted during the week. Furthermore, Hunt fails to take into account that the NHS is not dependent on just doctors. In order to have a service that operates fully throughout the week, the entire staff (doctors, nurses, office staff, porters, therapists and technicians, among many) must be available. Currently, some tests conducted on the weekend are in fact done at the beginning of the working week, because technicians may not work weekends. Any reduced efficiency of the NHS on the weekend may therefore be partly attributed to delays in test results.

Personally, I believe that although the new contract may be designed with the intention to promote a better NHS, it fails to understand that medics have other commitments, within and outside of medicine. With this change in contract we are putting the future of the NHS at risk, which is why 98 per cent of junior doctors voted in favour of industrial action last December. Junior doctors are valuable to the NHS and are the future of medicine in the UK, and we should be proud of these individuals who commit to a long degree and training course in order to provide an excellent healthcare service to the country. Let us hope their voices are heard before any permanent damage is done.

Krishnaa Pandya is a 3rd year medical student at Fitzwilliam College.

Working on Saturdays will no longer be considered unsociable

SARAH BINNEY

The Wunderkammer: The Dawn of Curiosity in Europe

Hannah Wayment-Steele explores the roots of scientific inquiry

In the late 16th and early 17th century, as European society encountered more of the world through trade and exploration, Europe's nobility, scholars and physicians began to collect the new, strange items that arrived: fossils, giant polyhedral crystals, stuffed birds of paradise, unicorn horns, cats with wings, and more. All these items would be crammed together into one display, uncategorised: each item as astounding and irreducibly complex as the next and intended to dazzle the onlooker. In addition to natural items, collectors would include works of art crafted from nature, such as ivory carvings or statues made from coral. These collections were displayed in cabinets or rooms, such as the Hainhofer cabinet or Ferrante Imperato's famous collection. They became hugely popular with members of the upper class, who travelled far and wide to view them. The collections were known by several names, including the 'Wunderkammer', the 'Cabinet of Curiosities', or the 'Cabinet of the World'.

The age of the Wunderkammer is the predawn before the Enlightenment. Although this practice of disordered collection may seem naïve and unsystematic from today's view, it formed the basis for many aspects of modern science. The Wunderkammer was European society's first glimpse into the wonder and endless variety of nature. It irrevocably aroused our curiosity about the natural world and helped shape a society that values scientific inquiry. Indeed, many aspects of the Wunderkammer have parallels with science today.

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Engraving from Ferrante Imperato's Dell'Historia Naturale (Naples 1599), showing the juxtaposition of many disparate objects typical for a Wunderkammer

In these times, due to the lack of scientific understanding, schemes used for categorising and deriving meaning in the objects differed from those used in modern museums. Displays were sometimes arranged to suggest metaphors beyond the objects themselves, often without scientific basis. For example, the Wunderkammer of Ferrante Imperato, an apothecary in Naples, had alternating rows of fish and starfish on the ceiling. Imperato intended to use the starfish to symbolise celestial bodies and to make reference to the idea that there are as many fish in the sea as stars in the sky.

Often aesthetics instead of scientific principles were primarily used to arrange the items. For example, one Wunderkammer had a drawer for 'bones', however, this included everything from an ivory sculpture to the arm bone of an ancestor. A painting by Isidore Leroy de Barde depicts a collection of shells, and although closer to a modern classification scheme, the collection is still arranged primarily on looks: from 'branched items' (coral, driftwood, and a large anemone) to shells categorised only by size. We eventually managed to better understand and categorise shells, but we still have modern-day Wunderkammern, packed with natural objects whose purpose we don't understand. For example, the 3,570 proteins classified as 'unknown function' in the Protein Data Bank. With time and better understanding, these will hopefully become clear to us too.

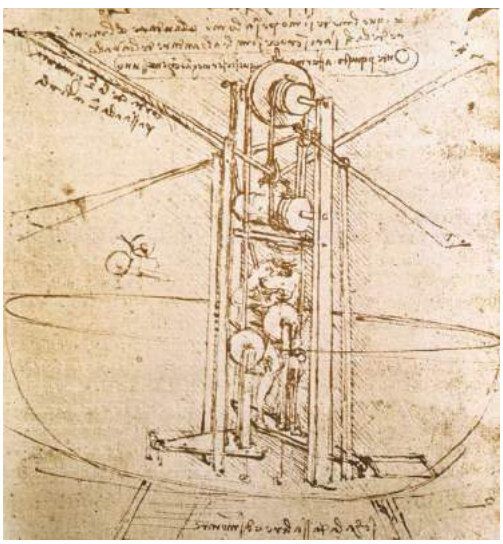
In addition to categorisation, the Wunderkammer also helped kindle the Western world's aesthetic appreciation of the natural world by blurring the distinction between art and nature. Previously, a


LOKILECH

A Wunderkammer on display in the Naturkundemuseum Berlin, dated to the early 18th century

boundary between art and nature had been set by Aristotle. But these new objects challenged this thinking - who was to tell if an intricate piece of coral was sculptured by nature or man? It had previously been thought that nature should be functional and practical, but there were now emerging colourful birds and ornate seashells that at the time appeared to serve no fathomable purpose. They reasoned their function was purely aesthetic and thus artists began using natural objects in their artwork. The old view that random natural variety was a deviation from the true order of things changed as natural variations were seen as artistic and potential sources of inspiration. Since that shift, nature has continually inspired us, not only in art but in technologies as well: from Da Vinci's flying machines, imitating bird wings, to superhydrophobic surfaces that imitate gingko leaves.

In our modern view of science, wonder and curiosity are natural partners, but these two concepts were not linked prior to the invention of the Wunderkammer. Before, curiosity had been a sin in the view of the Catholic Church. Wonder at the natural world was permissible, but to question it and be curious about it was an extension of lust – it was curiosity, after all, that expelled Adam and Eve from Eden. However, the influx of new inexplicable objects created insatiable curiosity amongst the upper class. The new objects seen in the Wunderkammer upended previously held views on the natural world. Was coral a vegetable or mineral? What mysterious process could create the imprint of a fish in stone and leave it on a mountainside? Curiosity thus had to be re-fashioned to be harmless: in 1620, Francis Bacon wrote that God regarded the investigation of nature as an "innocent and kindly sport of children playing at hide-and-seek". As scientific inquiry took off in the Enlightenment, curiosity was regarded as noble and essential to science as shown in a 1751 quotation from the philosopher Samuel Johnson: "Curiosity is, in great and generous minds, the first passion and the last." A look back at the Wunderkammer gives hope that our capacity for curiosity and wonder will enable us to continue solving our mysteries.


PUBLIC DOMAIN

Leonardo Da Vinci drew inspiration from nature for the design of his famous flying machines

Hannah Wayment-Steele is an MPhil student in the Department of Chemistry.

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ELIZA WOLFSON

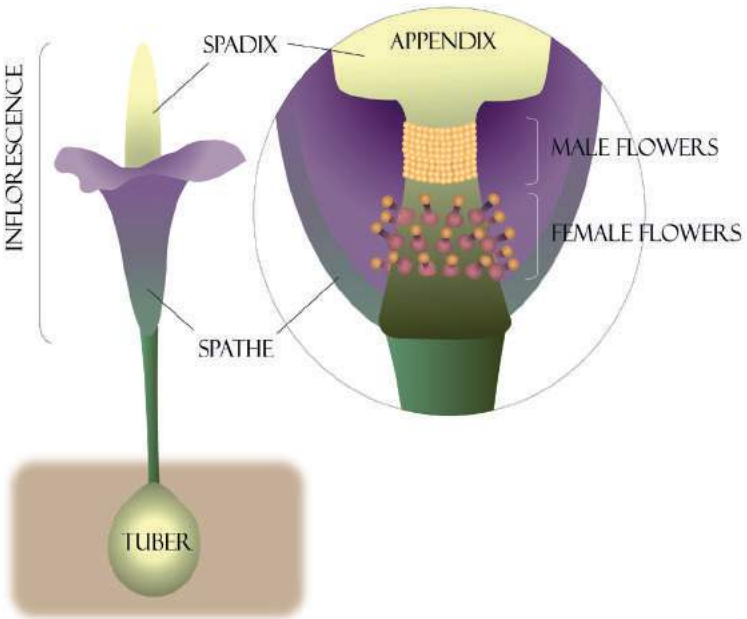
The Stench of Success?

Gwen Davies and Gabriela Doria discuss the recent blooming of the Titan Arum at the Botanical Gardens

Rotten flesh is one way you may describe the smell of titan arum in bloom. This summer 12,834 people visited the glasshouses of the Cambridge University Botanic Garden (CUBG) over five days with one objective: to experience the stench of the blossoming titan arum or 'corpse flower'. This was the first time in over 10 years that a specimen of titan arum bloomed at CUBG and a unique opportunity for the garden's visitors and researchers to explore the peculiar biology of this plant. In its native habitat in the undergrowth of tropical rainforests of Sumatra, the titan arum flowers every 10-14 years, lasting for two to three days. When the opportunity of one flowering on Cambridge's doorstep came around, there was a rush to learn as much as possible about this species. Whilst we have come a long way since thinking it was pollinated by elephants, this species is in so many ways still a mystery.

Titan arum is a member of the mostly tropical Araceae or Arum family, which comprises over 3,700 species ranging from the minuscule duckweed (*Lemna spp.*), to epiphytes with giant leaves like the Swiss cheese plant (*Monstera*). In spite of the enormous diversity in size and habitat, all *Araceae* are herbs with underground storage organs (tubers) and a characteristic cluster of flowers (inflorescence) consisting of a modified leaf (the spathe) which envelops a stalk-like organ carrying flowers (the spadix).

The structure of a mature Titan Arum, known as the 'corpse flower'



JESSICA MCHUGH

The scientific name of titan arum, *Amorphophallus titanum*, comes from ancient Greek roots and means 'giant misshapen penis'. This refers to the enormous phallic-shaped inflorescence, which can reach up to three metres in length. It is one of the largest flowering structures of the plant world. Each year, titan arum produces a single leaf up to seven metres tall, which has the appearance of a tree. The leaf nurtures the tuber before withering; a new leaf develops after a lengthy dormancy of several months. The inflorescence may replace the leaf in one season, feeding from the nutrients stored in the tuber. Whilst the inflorescence itself is enormous, the flowers are tiny, found only at the base of the spadix. In a single titan arum spadix there are about 500 male and some 450 female flowers. The remainder of the spadix, called the appendix, is bare of flowers. Typical pollinator-attracting organs (such as petals) are absent. The plant instead releases a distinctive scent of rotting flesh at night to attract pollinators (carrion flies or beetles). It offers no nectar reward to the pollinator and tricks it into visiting by mimicking decaying flesh, which the pollinator may use as a place to lay eggs. This deceptive mimicry is achieved by a mixture of traits. Crucial is the ability of titan arum to produce heat through chemical reactions, a process called thermogenesis. This heat may be produced to imitate the exothermic reaction of flesh decaying. Perhaps more importantly, however, it vaporises and distributes the rotten scent. The surface temperature of the inflorescence can reach up to 36°C in bursts or waves of heat. The large size of the inflorescence, sickly colour of the spadix, thermogenic heat production and distinctive carrion odour act together to convince a pollinator it is the genuine article. Drawn by these traits, the pollinators enter the inflorescence and travel to the base of the spadix. Once the pollinators enter the spathe chamber, any pollen they are carrying from other individuals will be released onto the female flowers as they travel down in search of 'rotting carrion'. When they reach the bottom of the inflorescence, the pollinators are dusted with pollen. They then leave the inflorescence and travel to pollinate another titan arum.

Researchers at CUBG and the Department of Plant

Thermal images of Titan Arum during flowering in the first night

Sciences are interested in the evolution and development of floral traits that are important in attracting animal pollinators. Understanding how these traits direct plant reproduction provides crucial information for the design of conservation strategies and for optimising pollinator attraction of cultivated plants. In their investigations they have found that the surface cell layer (epidermis) of a flower's petal is an important point of contact and provides visual, tactile, temperature and scent cues for the pollinator. The blooming of the titan arum was an opportunity to test the importance of these traits to pollinators in a highly unusual flower! Although the spathe in the titan arum is a modified leaf, not a petal, it plays a role as the point of plant-pollinator contact. With this in mind the epidermal cells on the inner surface of the spathe and on the spadix were imaged by researchers using scanning electron microscopy. These images were used to characterise the epidermal cells on those specific areas. The cells along the marginal area of the spathe are smooth, dome-shaped and very distinct from each other, whilst the cells at the base of the spathe, closer to the flowers, are flat and less defined. The mostly flat landscape of the surface of the spathe may provide little grip for the pollinators, causing them to slip to the centre of the inflorescence towards the flowers. Along the length of the spadix there are dispersed pores, which appear to be permanently open. The fetid scent of the titan arum is probably released through these pores. Having been secreted from these pores, the scent particles would then be vaporised and dispersed long distances by the thermogenic pulses produced from the spadix.

A series of thermal images were taken of the CUBG Titan Arum during flowering, and a timelapse movie was produced (see this at http://tinyurl.com/nlwltn4). The data collected from these images aim to estimate radiative flux coming from the spadix and to characterise the waves of heat production. This is important to understand the potential functions of heating the inflorescence during pollination. The heat begins from the tip of the spadix, where it also remains most intense. This may help overcome the vertical thermal variations of the night-time forest, which might prevent mixing of particles and therefore the scent dispersal. The thermogenic heating, especially at the tip, may allow the spadix to act like a natural 'chimney', thereby spreading the scent long distances. However, this thermogenesis occurs only on the first night of flowering, a surprising finding. It thus appears the inflorescence must rely on attracting all the pollinators it requires on one night. Another mysterious finding was that when the radiator in the greenhouse came on in the early hours of the morning, it stimulated an additional burst of heat from the spadix. Could it be that in its native environment, feedback from other closely located titan arum plants triggers simultaneous thermogenesis to maximise the chance of cross pollination?

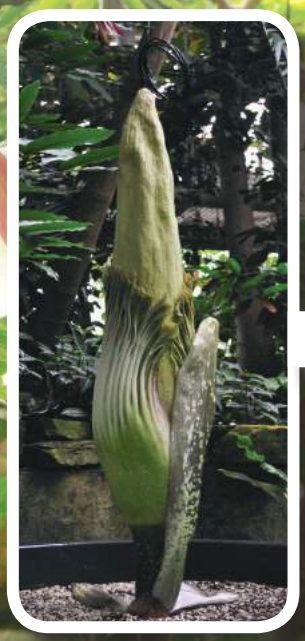
With infrequent, short-lived flowering and access to very few specimens, titan arum is a difficult but important species to study. Many aspects of its morphology, pollination and development remain a botanical mystery. This was the first time that the epidermis of the inflorescence of titan arum was explored, aiming to understand the role of microscopic features important in the interaction of this plant with its pollinators. The new record of thermogenesis of the plant growing in CUBG adds to the discussion of the regulating function of heating in this species and to the understanding of its pollination, but there is still much to learn. Unravelling more of titan arum's mysteries will help us to elucidate how this plant has evolved to maximise the efficiency of pollinator attraction. Knowledge which could be applied in conservation and cultivation strategies for this and other plant species.

With thanks to Professor Clive Oppenheimer (Department of Geography), Dr Edwige Moyroud (Department of Plant Sciences) and Professor Beverley Glover (CUBG).

Gwen Davis and Gabriela Doria are PhD Students in the Department of Plant Sciences.

12,834 people visited Cambridge University Botanical Gardens to see this event

A closer glimpse at the corpse flower!



Young inflorescence of Titan Arum. The blotched patterns of the stalk and leaves have earned the plant common names such as "snake-plant" and "devil's tongue"

The surface of the spadix has pores

The flowers of Titan Arum are tiny and confined to the very base of the spadix

The cells at the top of the spathe are dome shaped

The cells at the bottom of the spathe are flat

12,834 people visited Cambridge University Botanical Gardens, attracted by the rare stench of rotting flesh of the Titan Arum in full bloom

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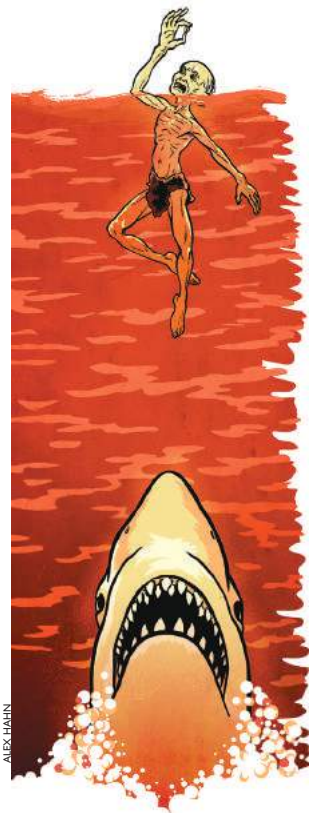
Weird and Wonderful

A selection of the wackiest research in the world of science


ALEX HAHN

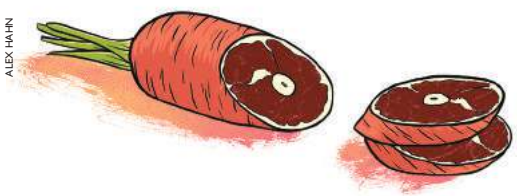
Active Volcano: Mortal Danger or a Shark's Humble Abode?

Sharks swimming inside an active underwater volcano: a scenario well-suited to the next James Bond film. Remarkably, this striking scene was brought to life when Brennan Philips led his expedition team to the Solomon Islands in the Southwest Pacific. The team originally set out to learn more about Kavachi: an active underwater volcano in the area. In order to observe the volcanos activity, they deployed various instruments, including a deep-sea camera, into its crater. After recovering the footage, the team watched in delight as jellyfish and a stingray were followed by both hammerhead and silky sharks onscreen. The waters surrounding the volcano are far too hot and acidic for human divers, so this surprising discovery raises questions about how these magnificent creatures are able to survive in such an extreme environment. In order to answer these questions, Philips is keen to monitor the behaviour of the animals alongside the activity of the volcano by pairing a seismic observatory with long-term deep-sea cameras. It is possible that the animals have developed an early warning system to escape the crater before it explodes. Otherwise, they would perish in the steam and lava... could they be heading for a great white-out? **KD**


ALEX HAHN

How Many People Live Within You?

You may have heard of the strange case of Lydia Fairchild, the woman who had her own twin within her. No one was more surprised than her when, in 2002, she found out that the two children she had borne were not genetically hers, but those of an unborn sibling whose cells she carried. Over a decade later, we now know a lot more about chimerism, the phenomenon whereby a single organism is composed of genetically different cells. But how common is this astonishing concept? There are many ways in which someone elses cells can become incorporated into our bodies. Foetuses, for example, can merge; exchanging cells between twins or picking up cells left in the womb by older siblings. Stranger still, a study by Dr William Chan from the University of Alberta onthe brain tissue of 59 deceased female subjects showed that 63 per cent were harbouring male Y chromosome DNA. These DNA molecules are believed to have crossed the placenta from male foetuses the women had carried, and become lodged in their brains. Curiously, women with Alzheimers disease displayed a lower prevalence and concentration of this microchimerism. The possible implications of chimerism are endless. We know that the gut biome can release neurotransmitters to sway your mood. Latent T. gondii infections, for example, are possibly associated with increased risk of schizophrenia and depression. What effects could those cells we thought were our own have? **JG**


ALEX HAHN

Synthetic Meat

What if processed meat was the healthiest and most environmentally-friendly type of meat? In a society where organic, natural and local is recommended, this might seem counter-intuitive. But with rapidly increasing global demand for meat, our livestock is raised with more hormones and antibiotics to boost yield, and uses more and more of our water and land resources. Spotting an opportunity, a handful of biotechnology companies have begun developing food products that could be alternatives to meat. The world's first lab-grown burger, which was engineered from cow cells ina lab in the Netherlands, got mixed reviews when it was tasted in 2013 and did not foster the expected enthusiasm. However, today many other promising projects are running: a company called Impossible Foods is hoping to have vegetarian steaks on the market by 2016. These steaks will not be traditional veggie or Quorn patties. They will have the taste of real meat due to the fats, proteins and other nutrients separated and drawn from various plants, grains and legumes combined with amino acids making them as close to meat as possible. This project, which received support from Microsoft founder Bill Gates, could define the future of our diets: environmentally-friendly plant-based meat. **AM**

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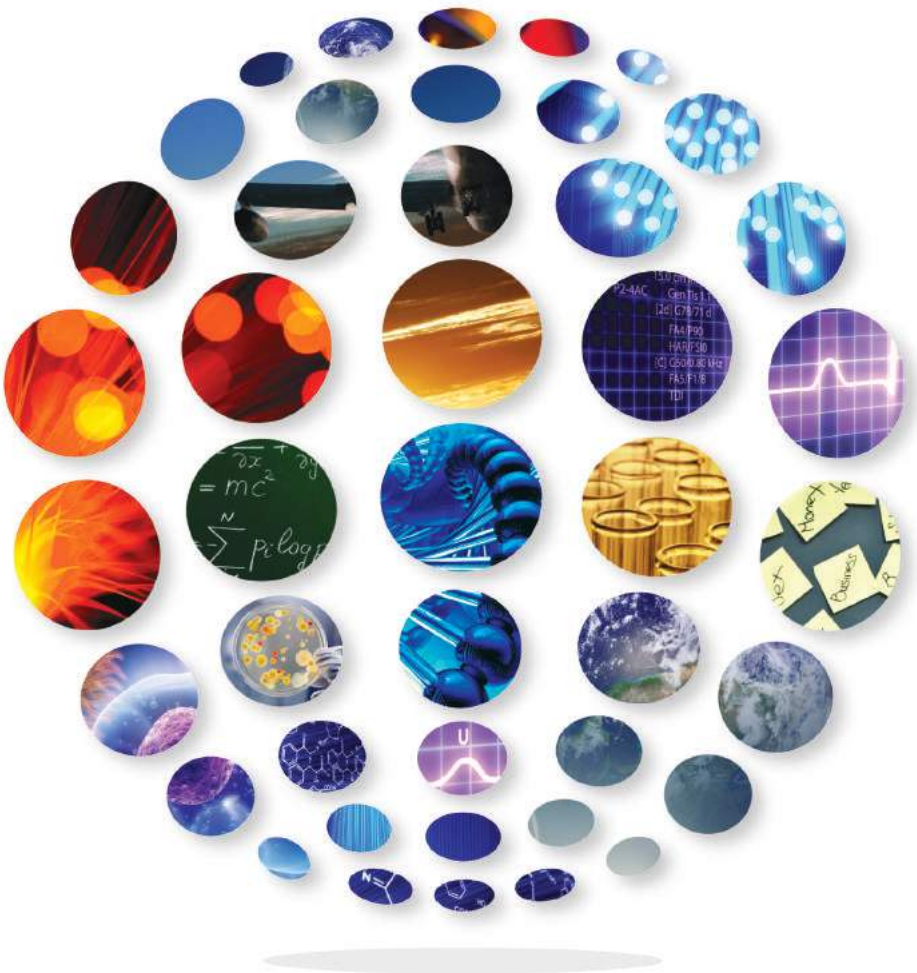

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