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Cambridge University science magazine

Michaelmas 2015
Issue 34

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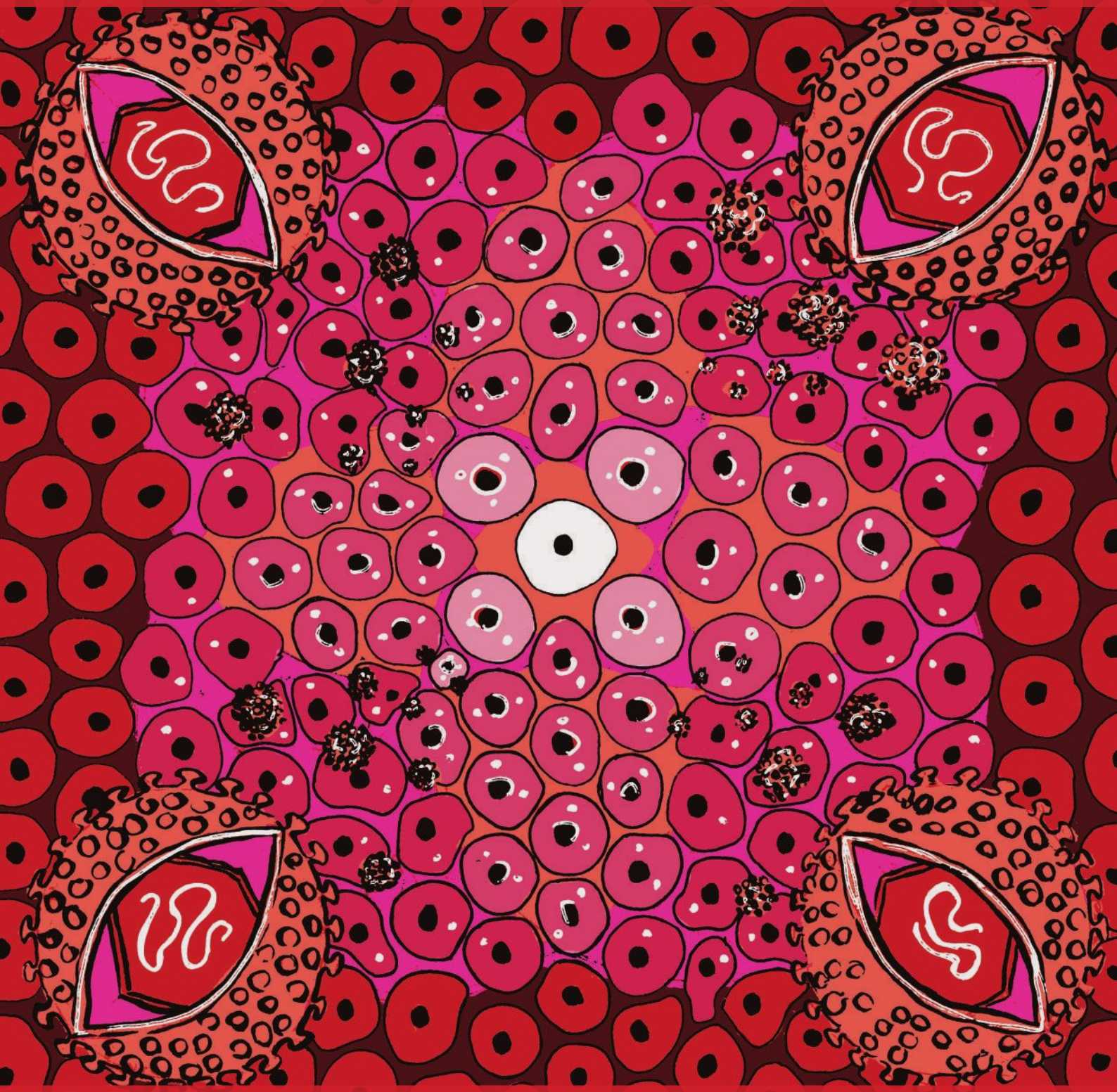

FOCUS

iPSCs: the future of medicine?

Fracking • Exoplanets • Perfumery

Athene Donald • Pluto • iChip

BlueSci
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BlueSci

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 34: Michaelmas 2015

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Cover Image: Claudia Stocker

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CUSU Cambridge University Students' Union

Breaking the Mould

10 YEARS AGO, two Japanese scientists were on the brink of revealing a discovery that would change the face of science and medicine. Once just a pipe dream, Shinya Yamanaka and his graduate student, Kazutoshi Takahashi, managed to reprogram specialised cells into stem cells using the simplest of laboratory techniques. This meant that any human cell could be produced from any other human cell, in a dish. The astounding finding of these 'induced pluripotent stem cells' and the great leaps that have been made in the study of diseases and in regenerative medicine since then, is the topic of this issue's FOCUS article.

Shinya Yamanaka 'broke the mould' with what some deemed to be an over-ambitious goal for his lab. His gamble paid off. In this issue of *BlueSci*, many articles encourage us to look at things from a different perspective. We discuss how we should evaluate different sides of important arguments in our feature on Fracking, and whether a knee-jerk reaction to join one side or the other is ever the best idea. In other features, we examine if we could, or would, actually use our microbiome for making food, and whether pollinators and nectar really have the harmonious relationship that we always thought they did.

Our Perspective article features interviews with Prof Dame Athene Donald and Prof Tim Bussey, both advocates for women in science. Their message is that we should to take action in the face of controversy instead of resorting to the obvious tactic of venting our frustrations on Twitter.

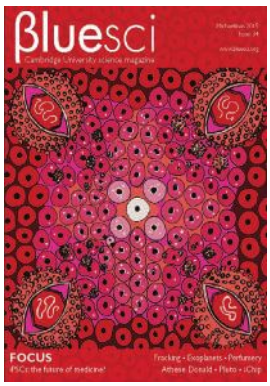
Pluto has astonished us all this summer. The Pavilion is a biography of our encounters with everyone's favourite dwarf planet, from the twinkle seen by the Hubble Space Telescope back in 1996 to the beautiful insights that the New Horizons mission provided us with in July. Despite no longer being 'one of the nine', Pluto is still defying our expectations.

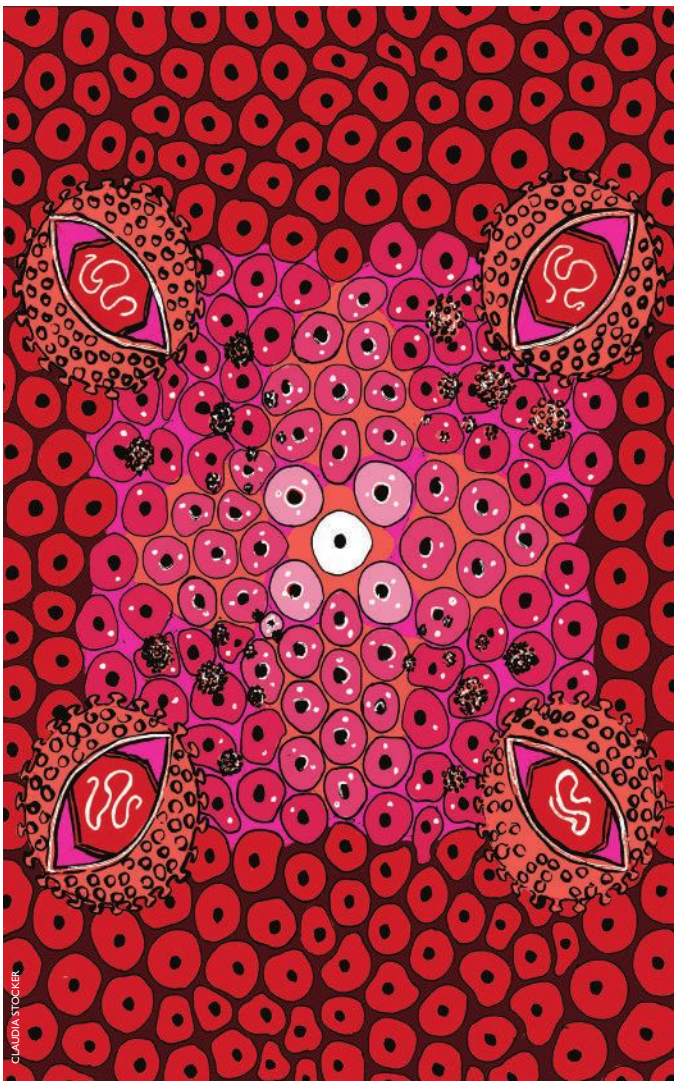
One thing that can always be anticipated, however, is the hard work and effort put into *BlueSci* by our writers, editors and producers. If you would like to be a part of the team and to have the opportunity to contribute to future issues, don't hesitate to get in contact!

"It is the tension between creativity and skepticism that has produced the stunning and unexpected findings of science" - Carl Sagan

Amy Danson
Issue 34 Editor

On the Cover





THIS ISSUE'S FRONT COVER showcases Claudia Stocker's illustration inspired by induced pluripotent stem cells (iPSCs), the FOCUS of this issue of *BlueSci* (p18).

"Looking at the focus article, I decided to concentrate on the biology behind how iPS cells are generated. So I read through Takahashi and Yamanaka's original paper and came up with an illustration involving the retroviruses that were used to induce the four factors required for reprogramming".

Claudia Stocker is a professional science illustrator who has worked with clients such as Mendeley, Square Kilometre Array and the Gurdon Institute. She works in London as a freelancer under the name Vivid Biology. She studied Natural Sciences at the University of Cambridge, completing an MSci in Systems Biology. This year she studied at the Royal Drawing School for six months on a scholarship.

Using her biological knowledge to underpin her creativity with scientific accuracy, she creates bold and schematic, visually arresting pieces as illustrations, info-graphics or animations.

"For me, engaging with the research and getting the details right is crucial. Sure you're allowed a bit of creative license, but a good solution shouldn't resort to incorrect science. I secretly double-check which way DNA spirals every time I draw it, just in case."

Claudia Stocker was commissioned by *BlueSci* to illustrate the cover with the scientific concepts behind induced pluripotent stem cells, discussed in the FOCUS section.

News


SUN LADDER

Breakthrough: Pancreatic Cancer Drugs

UCL RESEARCHERS have identified a new compound that shrinks and prevents the regrowth of pancreatic cancer tumours, one of the most fatal cancers. The drug, MM41, reduces the growth of pancreatic tumours in mice by 80%. MM41 targets knot-like structures in DNA known as quadruplexes, which are four-stranded configurations of DNA found commonly in human genomes, but prevalent in cancer cells. MM41 inhibits two genes: *BCL-2* and *KRAS*, which enable tumour cells to survive and divide. These genes are dysregulated in most pancreatic cancers and inhibition of their expression can cause cancer cell death. The team, led by Professor Stephen Neidle and funded by the Pancreatic Cancer Research Fund, conducted a trial on mice with pancreatic tumours. In the study, two groups of eight mice were treated with different doses of MM41 twelve times over 40 days, alongside a control group which received no treatment. In the group with a higher dose, tumour regrowth stopped in all mice within 30 days. None of the mice showed any side effects such as weight loss or damage to other tissues. With 7,500 new cases in the UK in 2013, pancreatic cancer is not a rare disease. However, prognosis for patients has not improved significantly over the past 40 years, and only 3-4% of sufferers will survive beyond 5 years. The current standard treatment, gemcitabine, results in only minor increases in life expectancy. Maggie Blanks, CEO of the Pancreatic Cancer Research Fund, said: "It's because of these bleak facts that our funding strategy focuses on finding and developing alternative, effective treatments for patients as well as finding a way to diagnose pancreatic cancer at an early stage. To find a potential new way to kill pancreatic cancer tumor cells is an exciting development". **RR**

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

Encoding Earth's Rotation

THE BIOLOGY of most organisms follows the 24h cycle of the Earth's rotation in order to adapt to daily changes. These so-called 'clock proteins' are transcriptional and translational regulators that have an oscillating activity and control the expression of other periodic factors (for example, testosterone or melanin). However, how this periodicity is encoded on the molecular level is unclear, since most biochemical reactions happen on a millisecond to minute scale. The collaborative effort of Japanese researchers has now found the molecular basis of circadian oscillation in the clock gene *KaiC* of the cyanobacterium *Synechococcus* elongates, which is the simplest organism with a circadian rhythm. Combining only three genes and ATP, the clock mechanisms of *S. elongates* can be modelled in vitro, and researchers found that by mutating the ATPase subunit KaiC1, they could create proteins with longer or shorter oscillating periods. Analysis of the crystal structure of the wild-type and mutated versions of KaiC1 helped them identify the reason the ATPase activity was so much slower than in other proteins: a water molecule close to the ideal position for ATP hydrolysis creates a steric hindrance and thus slows down the whole process. In mutants with a faster period, the water molecule was held in a more favourable position, while in slower mutants the water molecule was constricting the way to the hydrolytic centre even more. Additionally, the ATPase has to undergo a cis-trans isomerisation with high activation energy, slowing down the process even further. The natural frequency of KaiC1 alone was 0.91 +/- 0.1 per day, indicating that it was the speed governing factor in the complex. This study is the first one to show how a small protein molecule can generate a circadian rhythm on an atomic-scale level. **LS**

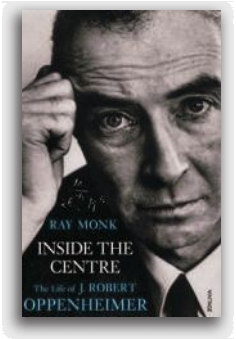
E-cigarettes: Good or Bad?


TBEC REVIEW

AS DIFFERENT STUDIES, industries and health experts continue to express different opinions, it seems hard to decide if they are a good or bad alternative to tobacco cigarettes as nicotine delivery devices. A multiple-article review cumulating data from over 2000 patients by scientists from the University of Toronto concluded that while e-cigarettes seem to help reduce smoking at 1 month, their efficacy for long-term smoking cessation is not evident. Furthermore, they found that e-cigarettes are associated with frequent short-term respiratory events; confirmed by a study at the University of Rochester and published in PLOS ONE, in which emissions from e-cigarette aerosols and flavorings created harmful free radicals and inflammation in lung tissue. With these results, it is hard to understand how tobacco companies shifting to e-cigarettes can claim that they are "part of the solution, not part of the problem". An investigation published in the British Medical Journal reveals that some health experts share this point of view, claiming that public health services and the tobacco industry should work together to support this "harm minimization" system. On the other hand, other specialists warned the WHO not to "buy into the tobacco industry's well-documented strategy of presenting itself as a partner." The tobacco industry has been accused of trying to appeal to underage consumers by flavorings including fruit, dessert, and candy. Health experts believe e-cigarettes entice some young people to start smoking and will make it socially acceptable again. Riyad al-Lehebi, the lead author of the meta-study of the University of Toronto summarizes a point of view shared by a majority of the medical community: "Until [more] data is available, there are a number of other smoking cessation aids available that have a more robust evidence base supporting their efficacy and safety." **AM**

Reviews

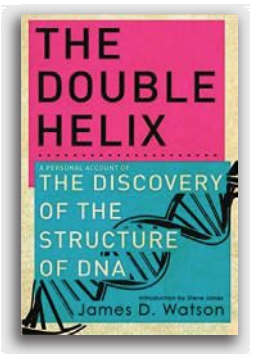
Inside The Centre: The Life of J. Robert Oppenheimer - Ray Monk



Anchor Books, 2014

This biography draws on a rich body of original material and personal testimonies, including Oppenheimer's own letters, to build up an excellent and comprehensive picture of the man who first gave atomic energy to humanity. The book begins with his privileged but unsettled childhood in New York's Upper East Side, and covers Oppenheimer's rise in the scientific community, his work on the atomic bomb, his alienation from the political establishment, his work in public engagement and concludes with his death. This book is most revealing of Oppenheimer's personal insecurities and complexities, particularly as regards his erratic episodes when jilted as a young man, and initially being patriotic and pro-war but resolutely pacifist after the atomic bombing of Japan, coupled with his longstanding political ambiguities. Monk highlights the persistent discomfort that Oppenheimer felt throughout his life in being Jewish, remaining serious in his analysis but never overly academic. The author competently discusses the science of Oppenheimer's work in early quantum physics, alongside the likes of Dirac and Born, and then his greatest contribution to physics, on black holes in general relativity. This is a meticulous and fascinating account of perhaps the most eminent and important scientist of modern times. **CB**

Double Helix - James D. Watson

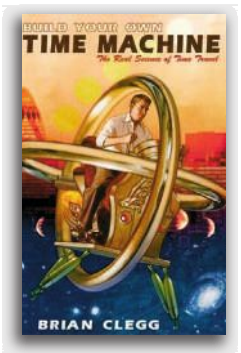


W&N, 2010

For all its controversial and polarising nuances (see: picking on poor "Rosy" amongst other things), The Double Helix still manages to provide a candid account of what is one of the 20th century's greatest scientific discoveries. In his book James Watson recounts the events surrounding the discovery of the structure of DNA, from the unassuming, almost sluggish beginnings, through to the frenzied race to the finish line. Watson tells the story from the point of view of his younger self, contemporaneous with the events narrated, but sprinkled with insight gained from later times.

The book is an interesting read for those curious about the events that allowed such a significant discovery to be made. It sheds light on why amongst all those involved in the race, Watson's team emerged victorious. What is even more captivating is Watson's genuine recounting of his thoughts and feelings at the time. The emotional ups and downs encountered throughout the journey are strongly relatable and inspirational at times. It leads one to realise that even seemingly impossible things can be made possible with the right combination of tenacity, intelligence and serendipity. **SS**

Build Your Own Time Machine - Brian Clegg



Gerald Duckworth & Co. Ltd., 2013

I dropped physics as soon as I could at school, but space was always something that fascinated me. I put it on the back-burner during my biochemistry degree until,whilst Christmas shopping in Heffers, this book caught my eye. Time travel has sparked the imagination of writers throughout the centuries; this book claims to answer questions like 'why wouldn't H.G.Wells's time machine have worked?' and 'what would we need to do to make a real one?'

After surreptitiously stealing it back from my brother straight after Christmas dinner, I discovered that this book was a beautiful biography of physics, wrapped up in the tantalisingly plausible fantasy of time travel. It describes, with complete clarity, particularly for the interested lay-person, the life and work of numerous wellknown (and some lesser-known) physicists, such as Nikola Tesla and Michio Kaku, as well as the concepts they developed. I found myself enthusiastically telling my physicist friends, much to their amusement, how I could now explain black holes and string theory. Clegg's in-depth knowledge of the physics behind time travel theories is complemented by a plethora of sci-fi references, which he admits was a big influence. Not for experts, but a very entertaining read. **AFD**

Biome Baking

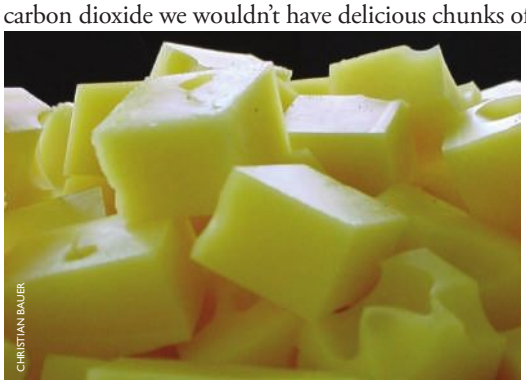
George Foot asks whether you would use your own microbes to make food

YOUR BODY is home to trillions of microorganisms. Outnumbering your own cells by a factor of 10 to 1, this ecosystem is known as your microbiome. Comprised of bacteria, archaea and fungi, it is fundamental to our existence, as a growing body of research keeps recognising the human microbiome's hugely diverse and beneficial nature. Nowhere is this more apparent than in the gut microbiome, which has been linked to aiding our digestion and protecting us from infection, diabetes and obesity. Food companies are now striving to understand more, and there is an increasing presence of foods that claim to help promote a healthier microbiome.

But what if these microbes could serve another purpose? What if they were intimately tied to the production of food? Say hello to one of the latest crazes of the food industry: making food from your personal microbiome. Think beard beer, vagina yogurt and body cheese!

Microbes are a crucial component of our current food system. Without microbes there would be no fermentation, and our ability to process raw ingredients, such as milk and barley, into some of the most widely consumed foods and beverages would be severely compromised.

Take one of the big guns: yeast. Without these single celled fungi breaking down glucose into ethanol and carbon dioxide we wouldn't have delicious chunks of breaded joy, nor would we have any form of alcohol. Chocolate would not exist either as it depends on the fermentation of cocoa seeds by yeast, filamentous fungi and bacteria. Vinegar, yogurt, pickles, cheese, soy sauce and saucisson would also be distant memories if we didn't use microbes in food production.


CHRISTIAN BAUER

Microbes are fundamental to the production of cheese as started cultures and to generate flavour through fermentation

Many of the techniques underpinning the processing of these foods have relied, unknowingly, on microorganisms for thousands of years. Wine has been produced for over 7,000 years and bread started being made with yeast in ancient Egypt 2,500 years ago. However, it wasn't until the mid-19th century that the importance of fungi and bacteria in the production of food and drink began to be understood. It still took another 100 years for the food industry to cotton on to the full potential of microorganisms.

Fast-forward to the present, and the food and drinks industry looks as though it might be developing a novel subculture. Pioneers have begun to create a range of cuisines using fungi and bacteria cultured from the nooks and crannies of the human body. I'm unaware of an official term for this type of food production, but I quite like the sound of 'biome baking'.

Cheese is one the obvious candidates for biome baking. There is a large diversity of culturable microbes colonising cheese that are fundamental to its production, as either starter cultures or generating flavour through fermentation. This includes fungi belonging to the *Penicillum* genus: *P. roqueforti* and *P. camemberti*, which are responsible for the blue in Roquefort and the rind of Camembert.

One project that has brought cheese biome baking into the news is Selfmade, a collaboration between scientist Christina Agapakis and artist Sissel Tolaas. Their exhibition was displayed at the Dublin Science Gallery and used human 'microbial sketches' to create a unique set of cheeses.

The cheeses were made from microorganisms collected from people's hands, armpit sweat and feet,

and included microbes from the tears of sculptor Olafur Eliasson, the bellybutton of chef Michael Pollan, and the nose of art curator Hans-Ulrich Obrist. The harvested microbes were inoculated into pasteurised milk and produced cheeses of varying odours, colours and textures, despite having been processed in exactly the same way.

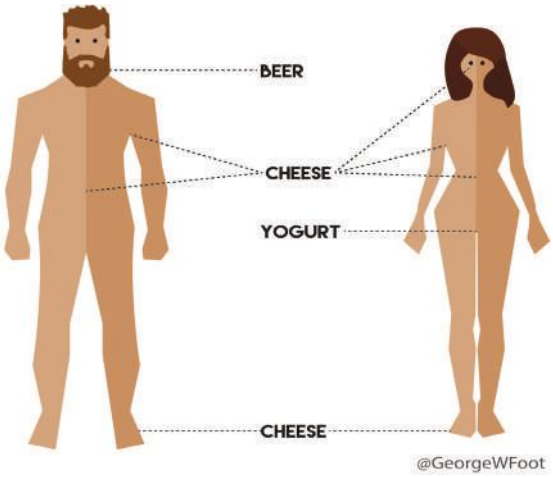
DNA sequencing of the biome cheeses revealed that whilst most of these bacteria are found in a variety of them, they also colonise some peculiar habitats. *Hafniaalvei,* swabbed from armpits, has been identified in human gastrointestinal tracts, faeces of the pygmy loris and the yellow catfish's stomach. *Proteus mirabilis*, swabbed from hands and feet, can colonise urogenital tracts and pig manure…

If you were getting excited about the prospects of genital Gouda or pygmy poo Parmesan, I have to break the news that the project wasn't to consume the cheese, but rather to explore our relationship with microbes. As Agapakis pondered, "Can knowledge and tolerance of bacterial cultures in our food improve tolerance of the bacteria on our bodies or in other parts of our life?"

One way to answer this question is being addressed by taking human microbiome consumption to new areas. Vagina yogurt is the love child of Cecilia Westbrook, a PhD student at the University of Wisconsin. Armed with a wooden spoon, some pasteurised milk and a thermometer, Westbrook produced a yogurt that she described as "sour, tangy, and almost tingly on the tongue".

While this does not sound particularly appealing, healthy vaginal flora is often dominated by species of *Lactobacillus*. This genus of bacteria is commonly used in the production of yogurt, and also has the advantage of producing antimicrobial substances that could protect against pathogens.

This experiment has certainly raised some interesting questions. If these are the same bacteria that are currently used in yogurt production, should they disgust you? Do you know where most of the microbes used in food production are cultured from anyway? Would you still eat your favourite cheese knowing that the bacteria could have come from pygmy Loris faeces or pig manure? If yogurt is made from bacteria of a healthy vagina, could the healthy status be taken as an



Bacteria used for food production can naturally be found in various places on the body

indication that it's good for us, and not something to be feared?

The Internet community were not so tolerant of the vagina yogurt project, with many expressing their disgust at the concept over social media, prompting Westbrook to shut the enterprise down. In an interview with *Jezebel*, she also questioned why people should react so negatively to the concept."People just seem really grossed out by the fact that stuff lives in there. But it's natural and part of your health. It seems weird to be grossed out about it."

A path to tolerance of biome baking may come from the drinks industry, one of the earliest industries to knowingly adopt the use of microbes. A prominent example comes from Rogue Ales, who produce a 'Beard Beer' from yeast that colonises the beard of their brew master, John Maier.

Should we really be more repulsed by vagina yogurt and armpit cheeses than we are of beard beer? Harmful microbes can come from any body surface, including beards. That would suggest that we should be wary of all forms of biome baking that don't employ rigorous screening of the bacteria and fungi they use.

Interestingly, however, our bodies shelter a surprising amount of microbes that have been used in food processing for thousands of years: *Saccharomyces* (beard), *Lactobacillus* (vagina) and *Enterococci* (armpit) all have long histories in food production. More foods than we probably realise have been created by the accidental inoculation by our own microbes. The use of these microbes in our dinners and drinks should not cause as much revulsion as it does.

Perhaps the time is not right for biome baking. It will take many more beard beers, innovators and research articles before it becomes accepted. But when it does, the results could be electric. Imagine a Kim Kardashian yogurt or the 'Great British Biome Bake Off'; it would certainly bring a whole new meaning to a soggy bottom…β

More foods than we probably realise have been created by the accidental inoculation by our own microbes

George Foot is a first year PhD student at the British Antarctic Survey (@GeorgeWFoot)

JESSICA MCHUGH

Fracking: Facts and Fiction

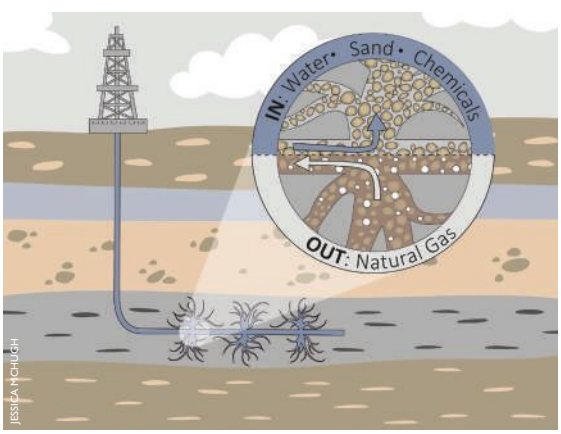
Ollie Stephenson explains why the fracking debate is far from simple

"I'm not a pessimist. I've always had a great deal of faith in people that we won't succumb to frenzy or rage or greed. That we'll figure out a solution without destroying the things that we love. I have not lost that sense."

So begins Josh Fox's 2010 film, *Gasland*, which shot the practice of hydraulic fracturing, or fracking, into the public spotlight. We're taken on a somewhat unnerving journey across the drilling rigs of America, past flaming drinking water, polluted air and billions and billions of dollars being made by some very smart people. With over 1 million wells fracked in the US alone, and the technology now being exported all over the world, it's safe to say that this is a big deal.

Depending on whom you ask, fracking is one of two things: either it is the sign of the end of times where fiery tap water and earthquakes will surely spell the end of humanity as we know it, or it is the new wonder technology, greener than Natalie Bennett frolicking in a grassy green field whilst wearing green clothes and promoting ambitious carbon reduction targets.

Unenlightening analogies aside, it must be said that for those who have spent much time looking into fracking there's a lot of noise, and even more money, being made. But let us start with a few reasonably uncontroversial facts.



High pressure water creates cracks off a main borehole to access trapped gas

Fracking is the use of high-pressure fluid in order to fracture rock, generally to increase the amount of oil or gas extracted from a well. As a technology it's not particularly new - it was first done in 1947 - but it is the modern application, using high volumes of fluid and horizontal boreholes extending for miles to extract gas from shale rock, which has caught the public's attention.

As the easily accessible resources have become depleted and energy prices have risen, the incentives to exploit trickier reserves have grown. In the early 2000s, these incentives drove oil and gas companies to begin drilling shale rock in the United States, a process made easier by the fact the landowners, rather than the state, own rights to oil and gas reserves under their land. Shale is an impermeable rock, which traps hydrocarbon reserves in small pores. If these are to be accessed, they need to be connected to each other and to the main borehole. This is where fracking comes in.

First, a borehole is dug vertically downwards until the rock containing the hydrocarbon is reached. In order to increase the area of rock that can be reached from one point on the surface, the borehole can then be dug horizontally for several kilometres through the target rock unit. Frackers then pump fluid at high pressures down into the well. The pressure creates a network of cracks off the main borehole, allowing trapped gas to flow from the rock up to the surface. Small particles of sand are added to the fluid to keep the cracks open when the pressure is removed. Chemicals are also added, for example to reduce viscosity and kill bacteria.

That's the basics of the technology, but where does the controversy come from? Simplifying the matter greatly, the central accusations

against fracking are threefold: 1) that it causes contamination of underground drinking water sources, 2) it gives rise to induced seismicity (earthquakes), 3) methane emission during gas collection and the burning of the gas contribute to greenhouse gases in the atmosphere and hence pesky, pesky global warming.

All of these issues are complicated and a detailed analysis would stretch to thousands of words. Has fracking resulted in water contamination? Yes, there are examples ranging from unreliable anecdotes to detailed studies that can easily be found online. Can this be avoided? Well, contamination can come from three places; leaking through the well casing, the propagation of fracking induced cracks from the borehole (normally several kilometres below the surface) to the water-carrying aquifer and mishandling of the wastewater produced by the process. But there is little evidence that cracks can propagate far enough to reach aquifers and that the contamination can be explained by poorly constructed well casings and bad environmental practices. Whether or not this can be totally eliminated is another question entirely, companies say yes, fracking opponents say no.

How about earthquakes? Fracking has been shown to cause induced micro-seismicity, i.e. very small earthquakes (equivalent to a heavy truck passing your house). Other human activities, such as coal mining and some kinds of geothermal power generation, can cause bigger earthquakes than this, but the thought of the ground under your feet being ripped apart due to huge volumes of water being pumped down there certainly doesn't lend itself to a peacefulnight's sleep or a stable house price.

Probably the largest problem is the emissions issue. As all good *Guardian* readers will know, climate change is 'The Biggest Story in the World' and it's safe to assume that anything accelerating climate change is likely to be bad.

Again the debates rage. On one side, advocates claim gas extracted from fracking acts as a useful bridge, cleaner than coal and giving us time to develop our greener options. Opponents are at pains to point out that 'cleaner than coal' is not a very high standard and that gas leaks during the process of drilling and extraction might actually cause fracking to have a worse impact than other, supposedly dirtier, technologies.

These controversies present us with an important question; when different groups of people who seem to not be obvious idiots have come to different conclusions after careful analysis of a complicated issue, what are we to make of this? It would seem prudent on our part not to rush to one side or the other, instead reserving judgement, considering conflicts of interest and proceeding with caution.

Water contamination, earthquakes and methane emissions are the main accusations against fracking

Gasland's focus on the human impacts of the fracking boom certainly has an emotional impact, but this can cloud our judgement and stop us asking important questions about the validity of the claims presented.Any subject which touches on energy will inevitably draw in a host of geopolitical issues, from shirtless Russian autocrats knocking on the doors of Eastern Europe, to the five Chinese coal fired power stations that have opened since you began this sentence. And where there is power, money and geopolitics, there is intellectual dishonesty liberally applied in the service of obtaining more power, more money and more geopolitical influence.

The economic benefits often touted by fracking proponents must be balanced against a careful analysis of the human and environmental impacts. But we must also accept that for every new technology there are those for whom it is just too advanced to be distinguished from magic, and thus to be distrusted.

This leaves not so much a conflict of interest as a giant battle: groups of scientists and politicians swayed by effective corporate lobbying versus groups of environmentalists with an axe to grind and a lack of peer review research. These people have the loudest voices and they polarise the debate. In between lie the inhabitants of a planet that looks not to be in great shape, hoping that a solution can be found "*without destroying the things that we love*". What is that solution? I don't know and I doubt you do either - let's work on it.

Ollie Stephenson is a 4th year undergraduate in the Department of Physics.


NESSALAND

Tears and Giggles

Jessica Farmery looks at why humans have evolved to laugh and cry.

HAVE YOU HEARD about the hyena that swallowed an Oxo cube? He became a laughing stock!

Did you chuckle? Or was that 'joke' tragic enough to bring a tear to your eye? The acts of laughing and crying are so commonplace and naturalised that we often don't question why such displays exist. From birth to death and across cultures, these behaviours are two fundamental mechanisms of human emotional exhibition.

So what is the origin of laughter and tears? Researchers in evolutionary biology propose that behaviours like these were selected for and maintained throughout evolution because they served a fitness-enhancing purpose. How then did laughter and crying enhance human fitness, and do they still serve the same purpose today? Perhaps their function has evolved to suit our new environment, or they may now be non-functional souvenirs of our ancestral past.

First, though, what exactly is laughter? The 'consciously controlled' laugh produced by humans is a pattern of exhalations used to punctuate speech and cement social relationships. Amongst orangutans, chimpanzees and gorillas, distinct types of panting, which could be described as 'laughter', are produced within the contexts of social play and tickling. Similarities in the acoustic features, including pitch, tone, volume and frequency, do indeed suggest a common evolutionary origin between these noises and human laughter.

Interestingly, humans seem to be the only creatures who laugh in response to a broad range of stimuli and across a wide range of contexts. This may be because our upright posture and characteristic bipedalism (walking and standing on two legs) enhances diaphragm control, and enables the necessary breath control for laughter and speech. Nevertheless, it is reasonable to assume that human laughter originated from ancestral primate displays and that, due to its comparably reduced complexity, it predated speech. The unique features of human laughter suggest that the trait was selected for and underwent further evolution after the human lineage first split from the chimpanzee lineage, our closest living primate relatives.

How, though, do we explain our need to laugh? The 'Social Brain Hypothesis' offers one explanation of why laughter evolved to become a staple of human social interaction. It proposes that the human brain increased in size and complexity to allow the formation of large communities rather than small bands. To prosper in these multi-person groups, individuals needed to be able to keep track of relationships, personalities and histories of prior interactions. They also needed ways in which to communicate and maintain group cohesion and inter-personal relationships.

Amongst our primate ancestors and today's non-human primates, participation in grooming activities (such as flea-removal) is the main way for individuals to bond and maintain social relationships. However, grooming involves only two individuals at a time, and thus constrains the ability to form wider alliances and relationships. Thus, speech may have evolved as an alternative mechanism for allowing communication and social interaction between larger groups of individuals. Even so, conversational groups are limited to about ten people by the practicalities of holding conversations; how then did human social groups exceed this number, as they would have done even before the emergence of villages and tribal organisation?

Researchers propose laughter has been evolutionarily selected for and maintained

ELIZA WOLFSON

This is where laughter fits in. Laughing together creates and reinforces bonds of social solidarity, and enables cohesion on a grand scale. There is no limit as to the number of individuals who can participate in group laughter. Just think of the large crowds filling arenas when comedians such as Peter Kay or Michael McIntyre hold sell-out tours. And, of course, laughter is undoubtedly contagious, which is why sitcoms so often have canned laughter to persuade the audience that the show is funny. The difficulty of keeping a straight face when you catch the eye of someone in hysterics perhaps indicates the strength of social cohesion encouraged by group laughter.

From another perspective, laughter provides a release mechanism for social or psychological tension. This would certainly explain why we sometimes laugh uncontrollably in formal or serious situations, for example, being told off, or maybe even during a funeral! The excess electrical activity in the brain is channelled to the areas responsible for sound production, and manifested as giggling or laughter. This re-direction of mental activation may also explain why spontaneous laughter usually results from a gradual build-up of expectation followed by a sudden anti-climax or twist. This is perfectly exemplified by most of the jokes told by comedians; you are unlikely to laugh twice at the same joke, because the punch-line is no longer a surprise. Following the same logic, the 'False Alarm' theory of laughter proposes that we laugh when a potentially threatening situation is diffused and our 'mental energy' is rapidly re-directed. The loud, explosive noise serves to inform others that the threat has been averted. What's more, laughter also appears to be good for your health. When you laugh spontaneously, hormones and chemicals called endorphins are released into the bloodstream, and can dull pain, improve the mood and reduce stress.

Whilst laughing is most commonly associated with happiness, the act of crying is usually perceived to be an indication of sadness. However, this response is not restricted to negative emotions; in fact, crying may also provide a similar release mechanism to laughter. Emotions that trigger tears include shock, relief, joy, anger or frustration, which explains why we may tear up when listening to music, watching films or viewing particularly moving images.

Humans appear to be the only creatures that produce tears, sobs, nose-streaming and upper-body spasms, which together are known as 'crying', in response to emotional or psychological triggers. Although a number of animals are capable of producing tears, termed 'lacrimation', these 'basal' tears are non-emotional. Instead, their functions include moistening the eyeballs and clearing the eye sockets of bacteria and dust. The tears also contain enzymes called lysozymes, which fight off bacterial infection. 'Reflex' tears are produced in humans and a number of other mammals as soothing response to eye irritation, for example the chemicals released from chopped onions.

Laughter creates and reinforces bonds of social solidarity

On the other hand, tears produced during emotional crying have a different chemical composition. They contain significantly greater quantities of prolactin, leucine-enkephalin and adrenocorticotropic hormones, as well as the elements potassium and manganese. The removal of the adrenocorticotropic stress hormone in tears may explain why people often 'feel better' after crying, and suggests that crying may have evolved as a mechanism to dispose of this potentially harmful hormone when its levels start to rise. Trials have suggested that the hormones in tears can also inhibit testosterone production, perhaps thereby reducing aggressive behaviour.

One theory on the emergence of emotional crying, advanced by Michael Trimble of the Institute of Neurology, is connected with the dawning of self-consciousness and the development of a 'theory of mind', when early humans first realised their peers were also self-conscious beings. He has argued that both laughter and crying represent the reduced remnants of the innate call system utilised by our primate ancestors. If this is so, then these 'calls' can be considered to be an important bridge between innate and learned vocalisations, and could even provide clues as to the origin of spoken language in humans.

The acts of laughter and crying amongst humans are clearly complex and fascinating phenomena. More in-depth study of these emotional expressions will shed some light on our unique evolutionary history, how our social systems developed, and the way our brains are wired. Rather than dismissing our laughs and tears as curious relics of our evolutionary history or trivial behavioural quirks, we must acknowledge that they are highly efficient tools for social interaction, communication and inter-personal bonding: surely no laughing matter! β

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PUBLIC DOMAIN

Nectar: Elixir or Poison?

Emily Marr explores the relationship between plants and their pollinators

THE CHEMICAL CORNUCOPIA of plants is a territory of which we have scarcely scraped the surface. Each part of a plant, from the nectar and pollen to the leaves, petals and roots, has a specific chemical composition. Furthermore, a plant's chemical signature may be inherited; the chemical signature of offspring is more similar to that of their parents than to that of other members of the species. This indicates that plant chemicals might undergo natural selection, depending on the advantage conferred to the plant.

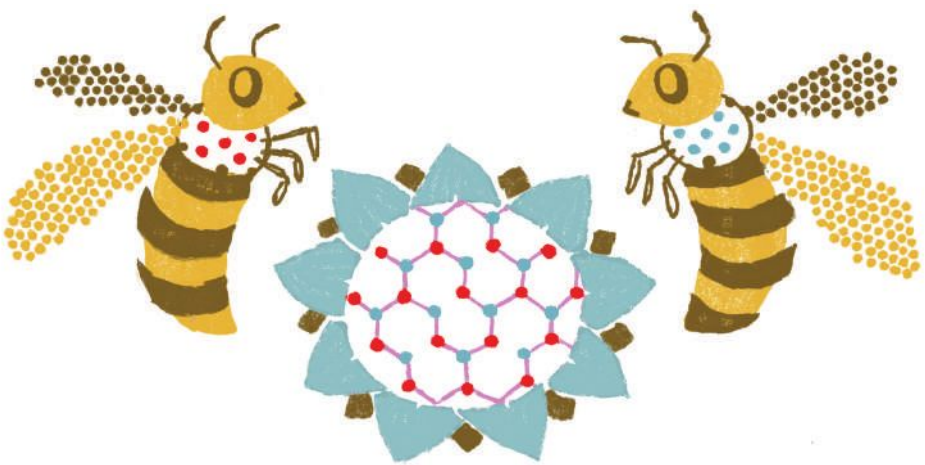
The relationship between pollinators and plants is often described as mutualism. Both partners benefit as the pollinator receives nutritional benefits and the plant is aided in sexual reproduction. Nevertheless, there may be a fine balance between cost and benefit. For example, it is in the interest of the plant to expend the minimum amount of energy in producing nectar whilst still maintaining pollinator activity. Thus, plants have evolved a specific nectar composition that exploits and optimises the pollinator's activity.

Common to all plants is the presence of sugars in the nectar. However, the identity and percentage of the sugar can vary. These sugars, for example, sucrose, fructose or glucose, provide a carbon source. Although lipids are more energy-dense than sugars, their presence in nectar is little recorded and they have been identified in only a few families, including the Iridaceae (Iris family), Krameriaceae, Malpighiaceae, Orchidaceae (Orchid family) and Scrophulariaceae (Figwort family). Amino acids provide a nitrogen source that is small but sufficient. Vitamins and minerals confer nutritional benefits with regard to metabolic processes.

The fascinating ability to manipulate the pollinator's physiology arises from secondary metabolites. Secondary metabolites are not involved in normal growth or development, but have other important roles that may affect an organism's fitness. Among the secondary metabolites we count the following classes: non-protein amino acids (NPAAs), alkaloids, flavonoids, isoprenoids and phenolics. In the context of bees, certain compounds are excitatory and boost pollinator activity. As this risks tiring them, nectar also contains calming compounds.

NPAAs are amino acids that are not genetically encoded and are an example of a class of secondary metabolites. For instance, ß-alanine acts as a neurostimulator and improves flight muscle activity. γ-aminobutyric acid (GABA) counteracts this as it is an inhibitory neurotransmitter whose accumulation renders the bee lethargic. GABA also acts on taste chemoreceptors with a phagostimulatory effect, causing the pollinators to seek more nectar. Moderating the activity of the bee may also be important in avoiding harmful alkaloid accumulation.

Alkaloids are a family of nitrogen-containing compounds, which include the well known morphine, caffeine and nicotine. Although toxic in high doses, alkaloids can be tolerated at the low levels found in nectar. Other parts of the plant, such as the leaves, can contain greater alkaloid concentrations as a defence



JOHN KARLEY

against herbivory. Alkaloids in nectar may have roles including encouraging specialist pollination, defence from nectar robbers and deterring inefficient pollinators.

Researchers at the Royal Botanic Gardens of Kew and Newcastle University have found that caffeine in coffea and citrus species improves the memory of honeybees for the floral scent of the flower from which they feed. Thus, the plant can spend less energy producing pollen as there is a greater likelihood of the pollen being delivered directly to a plant of the same species. Nectar robbers feed on nectar without collecting pollen. Alkaloids such as aconitine in *Aconitum napellus* (aconite) can deter these robbers. Bonafide pollinators feeding only on *Aconitum napellus* have a strong pressure to evolve resistance, for example by sequestering or excreting the alkaloid. In this case, the plant benefits from efficient pollen dissemination and the pollinator has reduced competition for its food source. In fact, whist pollinators may become resistant to alkaloids, humans previously unexposed to the toxins may succumb. In 400 BC, Xenophon of Athens described the effect of 'maddening honey' derived from the nectar of Rhododendron species on soldiers who went "quite off their heads, and suffered from vomiting and diarrhoea, with a total inability to stand steady on their legs". Several centuries later, this honey was implicated in the massacre of the incapacitated troops of Pompey the Great in the expedition against Mithradates IV of 67 BC.

Nevertheless, there are intriguing cases of nectar being toxic to pollinators. For example, *Tilia* (lime tree) nectar contains the sugar mannose that bumblebees cannot fully metabolise as they lack the enzyme mannose phosphate isomerase. Thus, the bees accumulate mannose phosphate and become paralysed. Honeybees, however, are not affected, even though their contribution to pollination seems to be no greater


BENGT NYMAN


ALREADYEXIST

Lime tree pollen can leave bees intoxicated, with some species acting as a narcotic

than that of bumblebees. In some cases, pleiotropic effects could explain nectar toxicity; that is to say, toxicity is not under selection but is a consequence of other traits that are under selection. Alternatively, the effect of toxicity may not be negative enough to be selected against. For example, bumblebees demonstrate no preference between a solution containing only sucrose and a solution containing sucrose and ecologically relevant levels of particular alkaloids. Failure to detect the taste of the alkaloid means that bees do not select against this trait when feeding.

For the pollinators that do survive, nectar can promote pollinator fitness by decreasing the parasite load. Alkaloids, isoprenoids, phenolics and flavonoids have been implicated in this role. They may upregulate the bee's immune response, promote endosymbiotic gut bacteria or perturb parasite development.

We often talk of particular plant species being 'good' for bees. What do we actually mean by good? Do they produce a lot of nectar? Do they contain a particularly beneficial cocktail of secondary metabolites? It is difficult to classify a particular nectar as good or bad. Rather, it seems that plants have differing degrees of toxicity and in some cases beneficial compounds compensate for or temper the negative effects of others. At certain concentrations a compound may be beneficial and at others it may be toxic. Furthermore, certain nectars may favour one species of bumblebee and be toxic to another. Is this a good or a bad plant for pollinators? A better understanding of the effect of nectar on pollinators could help us to select beneficial combinations of plants to have in our gardens and near crop land. Indeed, as we rely on insect pollinators for crop production, it is in our interest to maintain their populations. Variety may well be the answer as with greater biodiversity, positive and negative factors balance each other, wider nutritional sourcing is possible and pollination rates are more stable.

The winter aconite attracts bees and other pollinators but all its parts are poisonous to humans

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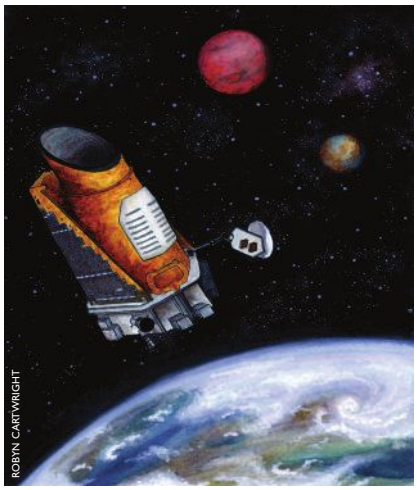

ROBYN CARTWRIGHT

Exoplanets: Lands Undiscovered

Susie Wright discusses the discovery of new planets outside of our solar system.

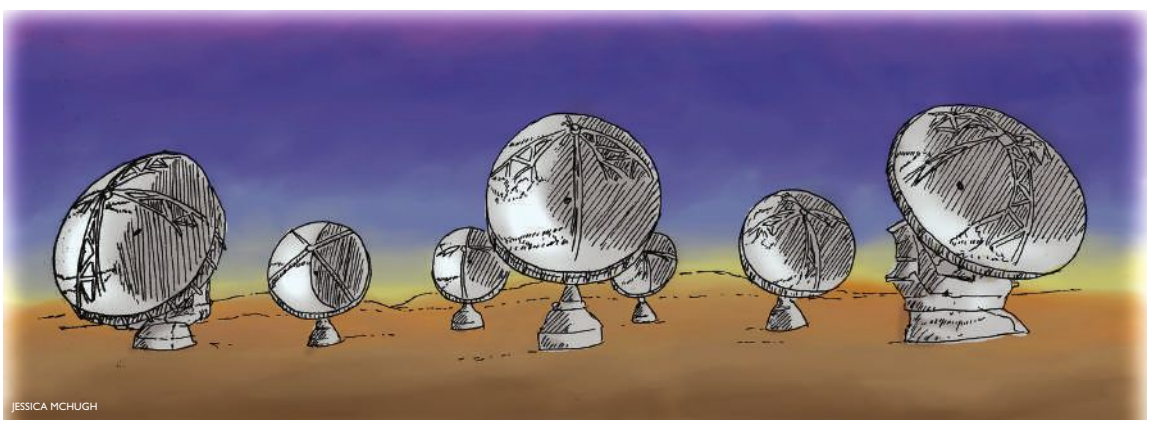
A LONG TIME AGO in a galaxy far, far away, a double sunrise awakens the desert planet of Tatooine, known to passing aliens as the cesspool of the universe. Of course, the home of Luke Skywalker is confined to the realms of fiction, as were all planets outside our own solar system until 20 years ago. The first discovery of an extra-solar planet, or exoplanet, was confirmed in 1995 and since then the rate of discovery has increased dramatically. To date, almost 2,000 exoplanets have been confirmed with a variety to rival even the Star Wars universe – from gas giants in binary systems to Earth-like terrestrial planets orbiting single stars.

The interest in exoplanet research is well founded. By combining elements of astrophysics, biology, chemistry and earth sciences, it is possible to predict the criteria for a planet to host life, which could be anything from single cells to any of the intelligent species invented by science fiction. These potential habitats for life exist in the so-called Goldilocks zone, a region at such a distance from its star that a planet is neither too hot nor too cold to have liquid water at its surface. Although the science of predicting an exoplanet's chemistry is in its infancy, in the last five years we have entered a golden age of planet detection, which has brought with it many possible candidates for hosting life.

Exoplanet science was revolutionised in 2009 with the launch of NASA's Kepler Space Telescope. Prior to this the main method used for planet detection was the radial velocity method. In a system containing a star and a planet, the two bodies orbit their combined centre of mass, meaning the star is not stationary, as a simple model might suggest. However, as the mass of the star is far greater than that of the planet, the star's motion is more of a wobble than a fully-fledged orbit. The wobble is detected on Earth using the fact that light emitted by objects moving towards or away from us has a slightly different frequency or colour. This 'Doppler shift' of red light when objects move away and blue-shift when it moves towards us results in a periodic change in the star's spectrum as the star moves away from and towards Earth.

Unfortunately, there are a number of problems associated with this method, one being that it yields relatively little information about the planet itself. The Doppler shift induced in the star's spectrum is greater for larger, closer orbiting planets. However, the shift only measures motion directly towards or away from the Earth. This means that we can only establish a lower limit on the mass of the planet, as if the orbital plane of the planet is inclined at an angle to the observer, the shifts will be smaller.

Another issue with radial velocity measurements is that they are influenced by a strong selection bias towards 'Hot Jupiter' planets. These are so-called


JESSICA MCHUGH

The next generation of telescopes: The Aracama Large Millimetre Array

because of their masses, which are similar to Jupiter's and their closeness to their stars, resulting in high surface temperatures. They are the easiest to find because larger planets closer to the star exert greater gravitational forces than those further away. However, these planets would be inhospitable for life and are thought to block the formation of Earth-like planets within the same systems, and so early planet searches were not fruitful as far as the quest for extra-terrestrial life is concerned.

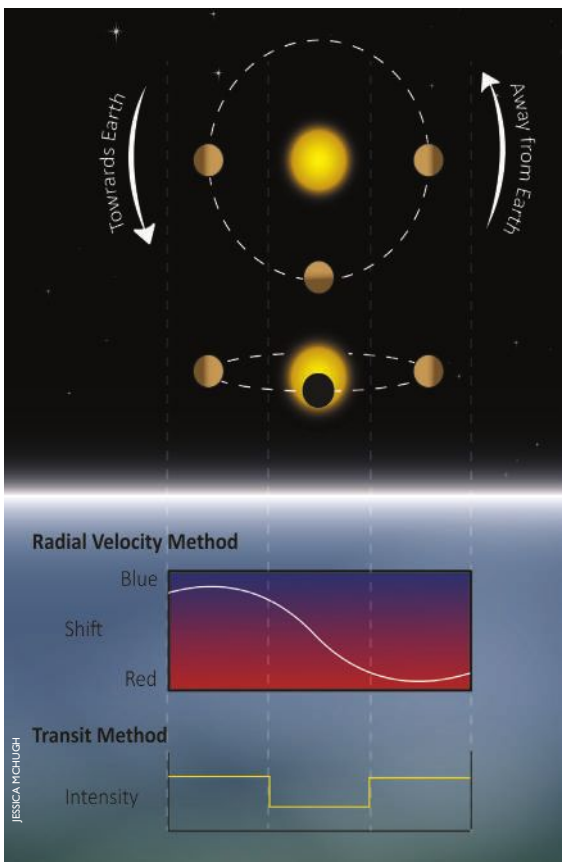
One of the aims of the Kepler spacecraft is to detect smaller, Earth-like planets within the Goldilocks zone and determine how frequently they occur. To do this, it employs a method less affected by the Hot Jupiter selection bias, known as the transit method. This involves detecting a periodic drop in the star's brightness as a planet passes between the star and the observer; a drop of about 0.01% for an Earth-sized planet. This decrease and frequency can be used to calculate the planet's diameter and the radius of its orbit. Once Kepler has found a potential planetary candidate, its existence is confirmed by the use of ground-based telescopes, perhaps employing the radial velocity method, or other planet detection techniques So far, Kepler has confirmed over 1000 exoplanets.

However, even with the advances brought by Kepler, we are still a long way from identifying many of the key properties of the planets that have been found. Even if a planet of suitable size is found within the Goldilocks zone, there is no guarantee that other environmental factors will provide a suitable habitat for life. While a few exoplanets have strong enough light signatures for us to analyse their atmospheres, successful measurements are still relatively rare. So, if we are not at a stage where we can predict the possible addresses of our alien neighbours, what new science has Kepler's detections produced?

Perhaps the most important advances have been made in theories of planet formation. Prior to exoplanet discoveries these theories were based solely on our solar system – imagine predicting the characteristics of all humans having only met one. Although it's difficult to account for selection biases, the general consensus is that our solar system is by no means typical.

In our solar system the smaller rocky planets are found closer to the star whilst the massive gas planets are at larger distances. However, a large number of closely orbiting Hot Jupiter exoplanets have now been discovered, as well as Earth-like exoplanets at greater distances. Planets form from a protoplanetary disk, a disk of gas and dust which surrounds a young star after its own formation. The most popular theory of planet formation involves collisions between small molecules and dust fragments, which grow into large boulders and eventually form planets due to gravity. The details of the process are greatly dependent on the environment of planet formation, for example, the amount of heavy elements present and frictional forces between the growing planet and the protoplanetary disk, which may cause the young planet to migrate towards the star. This is the theory of 'core accretion' and was historically favoured as it is successful in predicting many features of our solar system.

However, since the discovery of exoplanets, the competing theory of disk instability has been revived. It proposes that gas planets may form in a similar manner to stars. When a large cloud of gas becomes so large that the pressure within it can no longer withstand its own gravity, it collapses and fragments into numerous smaller, self-gravitating clumps which evolve into planets. Specifically, planets have been observed around stars containing a low fraction of heavy elements. Their existence is unlikely within the core accretion model but can be predicted by disk instability.



The radial velocity method and the transit method explained

Our ability to detect exoplanets has improved beyond recognition in the last 20 years and with the next generation of telescopes, such as the Atacama Large Millimetre Array, we may soon be able to identify the chemistry of individual planets. After that, it may not be long before we are sending intergalactic signals to communicate with Han Solo and co. or whoever else may be waiting on the many Earth-like planets we are predicted to find across the universe. β

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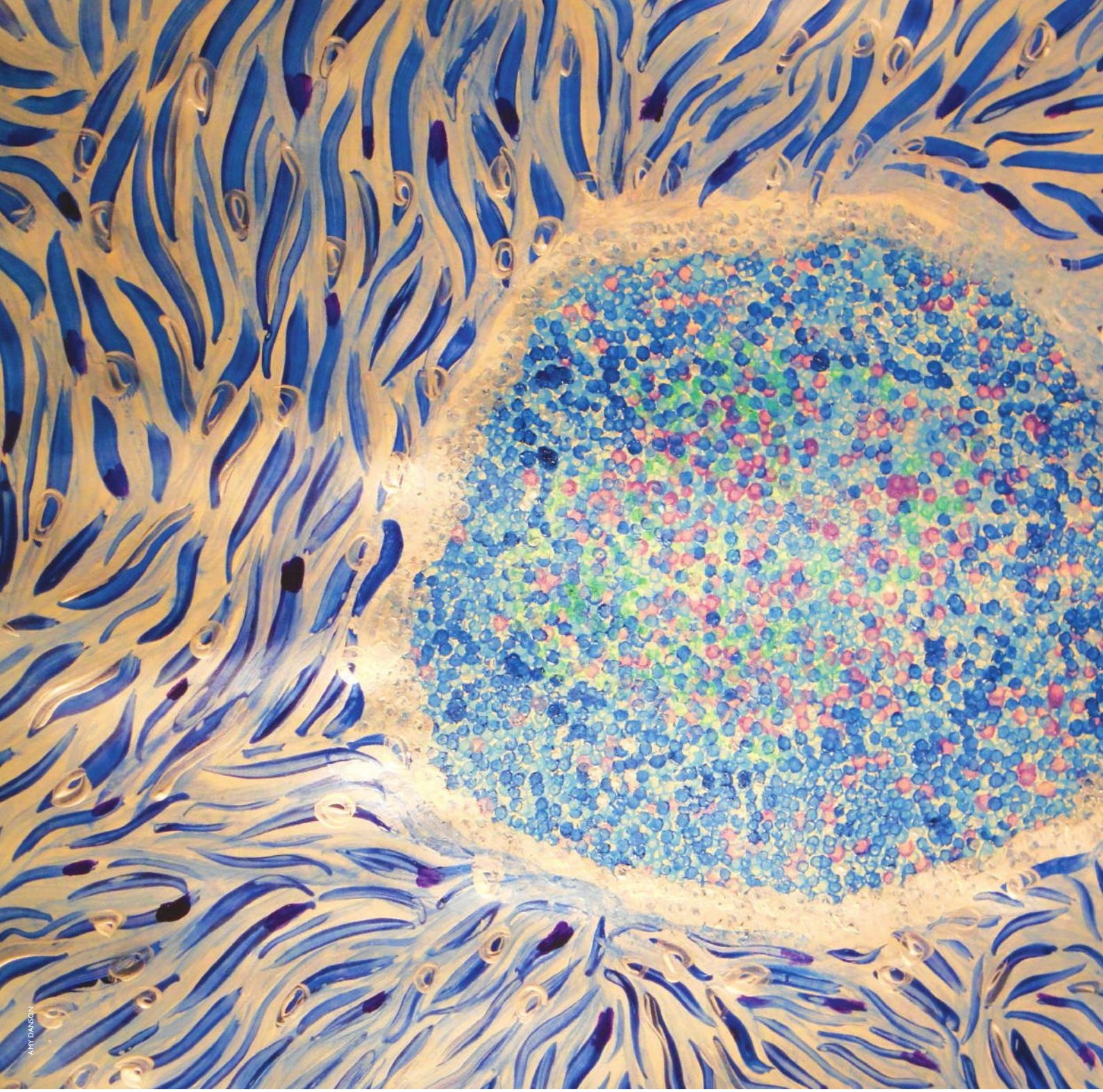


iPSCs: the future of medicine?

Artistic impression of an iPSC colony surrounded by fibroblast cells

BlueSci looks at how induced pluripotent stem cells were discovered and could be used to change the face of medicine

For centuries, alchemists and scholars have endeavoured to turn ordinary metals into gold. At the beginning of the 21st Century, the modern day equivalent – turning fully differentiated human cells (such as skin cells) into undifferentiated cells (i.e. 'stem cells') - seemed no less implausible. Yet 2016 will mark the tenth anniversary of a landmark paper, written by a group of Japanese scientists, which quickened the pulse of everyone in the stem cell field, earning them the Nobel Prize for Physiology and Medicine in 2012. By using viruses to express only four genes within differentiated cells, they created colonies of stem cells that could be turned into any cell type in the body (i.e. they became 'pluripotent'). They called these cells 'induced pluripotent stem cells' or iPSCs. Great leaps in disease research have already been made using these valuable tools, and the potential of iPSCs within regenerative medicine is beginning to be realised.

Stem cells are found in most multicellular organisms and have two key characteristics: self-renewal (being able to make identical copies of themselves) and pluripotency. There are pools of stem cells in the adult body which allow tissues, such as the skin and the intestines, to regenerate throughout life. Given the body's natural ability to regenerate certain tissues after injury or wear-and-tear, it is unsurprising that there has been a lot of interest in harnessing the power of stem cells.

The push for stem cell medicine is made more desperate by the chronic shortage of organ donations. Those lucky enough to receive life-saving transplants are still hampered by years of suffering on the immunosuppressive drugs required to prevent organ rejection. Using your own cells to repair or regenerate organs would be far preferable. But how do you go about acquiring enough of your own stem cells to, for example, create a whole new heart? Even if you cloned yourself, harvesting embryonic stem (ES) cells from the blastocyst for medical use has been ruled unethical, and is therefore not an option. But although we have known about tissue stem cells for decades, they are notoriously difficult to isolate and grow outside of the body; a necessary step to form them into a new organ, or repair an old one. So it seemed that, despite being so close, the hurdles were insurmountable.

As is often the case with Nobel Prize-winning discoveries, a combination of ingenuity and serendipity was required for a humble Japanese scientist to become a household name. A failed orthopaedic surgeon, Yamanaka held a number of

positions, before becoming a principle investigator at the Nara Institute of Science and Technology. On hearing that James Thomson's lab in the US had isolated human ES cells for the first time, he was inspired, seeing their potential in medicine. In a bid to attract graduate students to his fledging lab, he advertised his long-term goal as reprogramming somatic cells to ES-like cells. His ploy worked and Kazutoshi Takahashi, Eiko Kaiho, and Yoshimi Tokuzawa joined the lab.

Yamanaka's hypothesis was that by introducing specific transcription factors (i.e. ones that maintained pluripotency in mouse or human ES cells) into somatic cells, you may be able to reverse differentiation and induce pluripotency. They embarked on a mission to identify the factors required. In 2005, Yamanaka moved to Kyoto University; along with his factors, the assay system they had developed, and Kazu Takahashi. Kazu had his first paper published in *Nature* the previous year so Yamanaka had few worries about setting his graduate student off on what he knew to be a risky project. Kazu began by testing each of the 24 factors, one by one, using retroviral technology - a laborious and time consuming task. No single factor could reverse cell differentiation so Takahashi asked his supervisor if he could mix all 24 of the retroviruses. To his surprise, by doing this, he created colonies of cells that were very similar to mouse ES cell colonies. They didn't know, however, how many of the 24 would be necessary. Kazu proposed removing the factors one by one. In this, the breakthrough experiment, Takahashi found the four factors required to produce ES-like colonies, Oct3/4, Sox2, Klf4 and c-Myc, later named the 'Yamanka factors'. In the next year, they found they could do the same thing with human cells.

Shinya Yamanaka won the 2012 Nobel Prize for Physiology and Medicine for the discovery of iPSCs

Today, generating iPSCs starts with acquiring differentiated cells, which will later be reprogrammed. While it has been shown that it is possible to use many different cell types, the most common method, particularly when generating human iPSCs, is to obtain a skin biopsy. In this procedure a small section of skin, typically four millimetres in diameter, is taken and cultured. From this sample, a starting set of fibroblasts is generated.

In the traditional method that Yamanaka and Takahashi used, the four Yamanaka factor genes are carried within a viral genome, a lentivirus or retrovirus in particular. These viruses are capable of inserting their genetic material into the host cell genome, and it is this feature which is harnessed for the delivery of the Yamanaka factors. Once inserted into the genome, the genes are expressed using the host cells' machinery. This process has several drawbacks: it can lead to genetic alterations leaving marks known as 'genetic scars', expression of the factors can be uncontrolled and highly variable, and the method can lead to potentially cancerous behaviour in the cells.

In recent years, methods which do not require integration of the factors into the host cell genome have been developed, overcoming some of the drawbacks. These include using genetic sequences from non-integrative viruses, such as Sendai virus and Epstein-Barr virus. The viral sequences are eventually lost from the cells, leaving less of an impact on the host cell's genome. Another approach removes the need to introduce the Yamanaka factor genes as DNA by instead inserting them as mRNA. Alongside these alternative methods, it has recently been shown that using specific chemicals on cells expressing the Yamanaka factors can enhance the rate of reprogramming. However, the reprogramming procedure still remains inefficient and often produces cells that replicate at a rate similar to ES cells, but that do not possess the same differentiation potential. It is therefore important to assess whether cells are truly pluripotent.

The key feature of the iPSC is the ability to form all types of embryonic tissue. To test this, the iPSCs can be inserted into the blastocyst. If the cells go on to form the full range of cell types, the line is considered pluripotent. While feasible for mouse iPSCs, this test cannot be used for human lines. The closest similar experiment is to insert a human iPSC into a mouse teratoma and observe whether the iPSCs forms different tissue types within the tumour. However, other tests can be used as indicators of pluripotent stem cell nature.

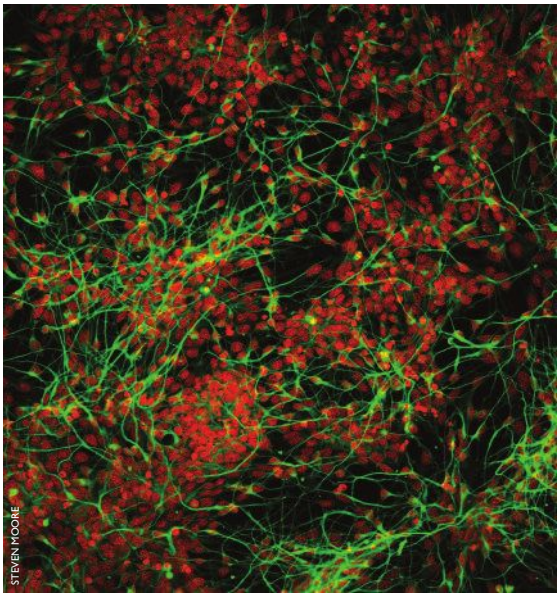
Examples of these include studying the appearance of the cells, monitoring replication rate and probing expression of marker genes that are normally expressed in ES cells.

Upon verification of pluripotency, the iPSC line is then grown and expanded. However, the cells may have the potential to differentiate in culture, so ensuring conditions are right to maintain the stem cell nature is important, but can prove difficult. Furthermore, animal-derived products are widely used in standard cell culture procedures, which has raised concerns if human iPSCs are to be used in therapies. Systems that do not use animal products have therefore been developed.

Owing to their capacity to both self-renew and differentiate into any specialised cell type, iPSCs can provide a limitless supply of cells whilst retaining the specific genetic signature of the donor patient. As well as advancing the field of regenerative medicine, this unique property is allowing scientists to shed new light on the mechanisms of disease and explore potential therapeutic avenues.

In order to successfully prevent and treat a disease we must first understand how it develops; a complex question that still remains unclear in many cases. Using patient-derived iPSCs to simulate disease, our knowledge of the molecular mechanisms of both monogenic and polygenic diseases has been, and continues to be, greatly expanded. Compared to traditional methods of using animals or adult cellular models, iPSCs present some considerable advantages in studying human disorders. While genetically engineered animal models have proven valuable in understanding disease mechanisms, many complex human diseases cannot be fully recapitulated across species. Furthermore, the cell type of interest may not be amenable to culture outside of the body, or may simply be inaccessible, as is the case for neural and cardiac tissue. With iPSC technology, patient-derived pluripotent cells can be deliberately guided to become any disease-associated cell type using specific combinations of growth factors and small molecules in the growth medium. Since the resulting differentiated cells carry the same genetic background as the patient they were derived from, this results in a replication of the patient's disease 'in a dish' and allows scientists to study how specific genetic mutations affect cell biology and function in an accessible *in vitro* setting.

Alzheimer's disease provides one such example for which modelling using iPSCs is having a significant impact. This complex neurodegenerative disease is the most common cause of dementia, currently affecting more than an estimated 44 million people worldwide. Given our ageing population, this number is predicted to more than triple by 2050. With no disease modifying treatments currently available, a clear understanding of the mechanisms underlying its initiation and progression is important. Dr Rick Livesey's laboratory, at The Wellcome Trust/Cancer Research UK Gurdon Institute at the University of Cambridge, have developed a method of guiding iPSCs, derived from skin cells from patients with Down's syndrome or inherited Alzheimer's disease, to become cortical neurons. The three-dimensional, electrically active networks that formed behave just like those of the human brain and develop hallmarks of the disease in a matter of months rather than years, allowing the disease to be modelled in a short period of time.



Human neurons (green) and neural progenitors (red) derived from iPSCs

"The ability to model Alzheimer's in human cortical neurons allows us to investigate how the early stages of the disease modify key cellular processes in a way that is not possible in patients or animals. This approach has the potential to identify pathways altered during Alzheimer's initiation and may provide new avenues for future therapies", said Dr Steven Moore, a post-doctoral researcher in Rick Livesey's laboratory. In a recent study, published in the journal *Cell Reports* in April 2015, this experimental model was successfully used by Dr. Moore and colleagues to reveal how three disease-associated proteins are linked in a biochemical pathway that controls Alzheimer's progression. Importantly, since both familial Alzheimer's and

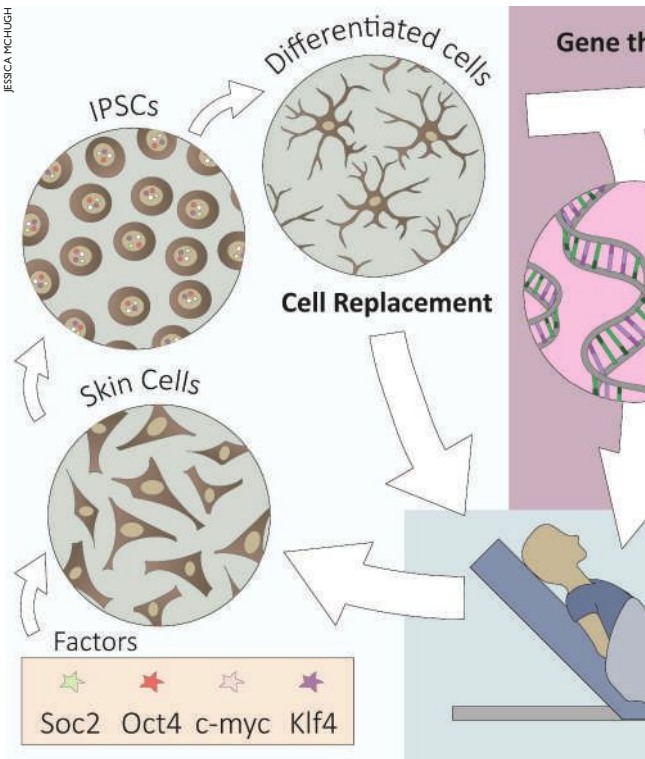
the more prominent sporadic cases display the same characteristic disease traits, these findings and the benefits that arise from them will be applicable to all patients.

iPSC-derived models also provide a powerful platform for the preclinical screening of drug candidates in a high-throughput manner. This not only reduces the number of animal experiments required in drug evaluation, but also enables new compounds to be tested on cells derived from real patients at an early stage in the drug discovery process. This is expected to give rise to an increased likelihood of successful translation from initial trials to the clinic, where currently later stage testing in patient populations lends itself to a high and expensive drug attrition rate. In addition to "drug effect", iPSCs provide a complementary system to animals and culture models in assessing "drug toxicity". Testing compounds against iPSC-derived cells from patients with a known drug response could allow scientists to pinpoint variables that make an individual more likely to react positively or adversely and hence help give the right drug to the right patient.

The processes of iPSC creation and use are still being developed

While neurodegenerative diseases have been an attractive target for disease modelling, in part due to well-established differentiation protocols, research into treating many other diseases is benefitting from this new technology. From heart disorders, to liver disorders such as Wilson's disease, to cystic fibrosis, the versatility of iPSCs is emerging. Furthermore, the use of iPSC technology is expanding to investigate infectious diseases. Currently this has been limited to the investigation of infection by viruses such as human immunodeficiency virus (HIV) and hepatitis C, however it has the potential to be adapted to other pathogens. For example in 2012, Finkbeiner and colleagues produced "induced human intestinal organoids", offering a promising model of rotavirus infection, the most common cause of gastroenteritis in infants. iPSC technology may also be beneficial to our understanding of the molecular mechanisms of cancer, with several studies now reporting the reprogramming of cancer cells to a pluripotent state. With the emergence of gene editing technologies, such as CRISPR-Cas9, the role of specific genes in such complex disorders can also now be investigated.

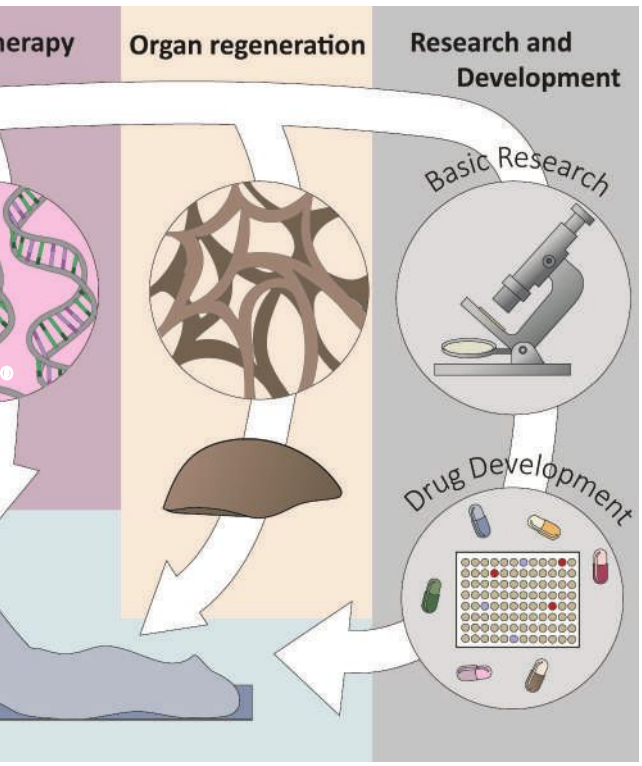
The advantages of iPSC in medicine don't end there. Shortly after their discovery, it was realised that these cells could actually be used to directly treat patients in cases where genetic mutations meant that certain populations of cells didn't function properly. The first steps towards this were made in Rudolf Jaenisch's lab. They used a humanised sickle-cell anaemia mouse model to show that mice could be rescued from the disease after transplantation with blood cells derived from iPSCs, created from the diseased mouse. This was achieved through correction of the mutation in the haemoglobin gene (beta-globin) by gene editing in the iPSCs. Scientists are now making further progress towards using iPSCs in regenerative medicine, for example for the treatment of Parkinson's disease, spinal cord injury and diabetes.



However, this type of 'cell therapy' has its pitfalls - more than 3 months are needed to generate iPSCs, so treatments like this would incur high medical costs. Using 'allogeneic' iPSC cell lines from donors may be an important alternative as there is the potential for a diverse array of donor candidates with multiple clones from each donor. The maturity of the differentiated iPSCs also needs to be considered. In order to replace beta-cells that are destroyed during diabetes, for example, the iPSC-derived cells would need to be able to secrete insulin. Similarly, in treatment of degenerative diseases, such as Alzheimer's disease, the transplanted cells would need to be mature enough to function in the place of the lost cell type. Integration of the iPSCs into the host tissue also

needs to be addressed: genetic changes that arise during the reprogramming of iPSCs may render iPSCs different enough to be rejected by the host upon transplantation, even if the cells derive from that patient.

Despite these hurdles, the first person to receive tissue generated from iPSCs was in September 2014. A team of eye specialists implanted a 1.3 by 3.0 mm sheet of retinal pigment epithelium cells (a supportive base layer of the retina), derived from iPSCs induced from the patient's skin, into an eye of a Japanese woman in her 70s. She suffers



from age-related macular degeneration, a condition where extra blood vessels form in the eye, which in turn destabilises the retinal pigment epithelium. The operation was performed days after a Health Ministry committee gave clearance for the human trial. Although the procedure is unlikely to restore the patient's vision, researchers around the world will be watching closely to see whether the cells are able to prevent further destruction of the retina, while avoiding potential side effects, such as bringing about an immune reaction or inducing cancerous growth. The research in Japan, led by Shinya Yamanaka, is ongoing and in February 2015, it was announced that Kyoto University Hospital will be opening an iPSC therapy centre in 2019 for the purpose of conducting clinical trials.

One of the main aspirations of improving iPSC technology is the ability to engineer whole organs, providing patient-derived replacements and overcoming donor shortages. The idea is theoretically simple: a scaffold, either artificially made or from a dead organ, is repopulated with stem cells from the patient and then transplanted. Most frequently, scaffolds are generated from pre-existing organs by cleaning with a detergent to remove cellular material, leaving just the extracellular matrix. The organ does not even have to be human; research on the use of pig organs shows promise as an alternative. Once created, the appropriate cells, which may be derived from iPSCs, can be applied to the scaffold. However, not only are most organs complex - requiring the generation of many specialised cell types in a precise manner - but the organs must be sterile, able to grow and repair themselves in the patient, and function for many years once transplanted. Despite these challenges, there has been considerable success with hollow organs such as tracheas and bladders, which are relatively simple, but the application to solid organs such as hearts and kidneys remains a future aim.

It is clear that, whilst there are still problems to overcome, iPSCs are the future of medicine. But in order for iPSC technology to reach its full potential, continued support of tissue donors, both disease sufferers and healthy 'control' individuals, is key. It is therefore vital that both patients and their families understand the huge scientific potential of iPSCs, and that any concerns are lessened by making sure the decision to donate is informed and consenting and that the process is as transparent as possible. The iPSC lines generated from such altruistic donations can then be banked and distributed to laboratories worldwide, aiding researchers in their quests to develop therapies for both current and future generations in the years to come.

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Glossary:

Blastocyst - the ball of cells formed early in human development

Extracellular matrix - a mesh of proteins and other structural molecules

Fibroblasts - cells which are found in the dermal layer of skin and are responsible for producing connective tissue

Monogenic/polygenic diseases - diseases regulated by one/ multiple genes

mRNA - an intermediate molecule in the production of protein

Organoids – spheres of cells grown in vitro which attempt to mimic organ structure and function

Teratoma – a cancer that derives from germ cells

Transcription factors – proteins which regulate the expression of a set of target genes


JOHN KARLEY

The Secrets of Scents

Rob Scanes explores the history of perfumery

HOLDING THE POWER to disgust or entrance, give a sense of place or ignite a long-dormant memory, it is unsurprising that harnessing smells has been big business for thousands of years. Records of perfume-making date back to the second millennium BCE, in Mesopotamia. Ancient Egypt was so renowned for it that when Julius Caesar conquered the nation, he returned to Rome in a parade throwing bottles of Egyptian fragrance to the crowd.

Perfumery in Britain reached a golden age through the Tudor and Stuart periods, as trade with the Islamic world had brought exposure to knowledge of chemistry and distillation. Although records are relatively scarce, one of the best accounts relates to the research laboratory set up by James IV of Scotland, who reigned from 1488 to 1513. His eccentricities led him to pay people to let him perform surgery on them. He loved chemistry and the lab he set up consumed huge quantities of mercury, silver, gold and alcohol in the quest for the philosopher's stone. However, most of the lab was for the preparation of aromatic substances, and cost hundreds of pounds per year to run. Records suggest that operations were scaled back following an event in 1507, when the chief alchemist, John Damian, told the French ambassador that he was to fly to Paris, and promptly jumped from the battlements of Stirling Castle. Surviving, but with a broken leg, he claimed that the feat had failed due to a workman incorporating hen's feathers instead of eagle's into his Icarus-style wings.


MAKEDOCREATIVE

Beaver testicles were once the source of musk

As courtly life declined, so did perfumery, and simpler measures were more popular in the 18th century, such as the carrying of dried flowers and herbs. Having said that, it was common among the gentry and aristocracy to have a dedicated distillery, or 'still room', in their houses for the production of plant extracts. These were used in cordials, curative gins, various cosmetics and cleaning products as well as perfumes. By this time, women usually governed the stills, with the housemaid running it, often teaching younger daughters of the house the skills so they may be more desirable wives, or employing older female relatives so they may remain within the household.

Perfumery has a reputation for being somewhat esoteric, but many of the words simply refer to concentration, the total amount of aromatic substance within the solvent, which is usually an ethanol-water solution. Generally, the most concentrated solutions are referred to as Eau de Parfum, followed by Eau de Toilette, followed by Eau de Cologne. Therefore, a parfum is not necessarily intended for a woman or a cologne intended for a man. These terms only became widely used in the 19th century, where increased demand for perfumes came from a burgeoning middle class, and for the first time standardised products produced by the chemists and druggists were available.

Another innovation of the Victorian era was that of synthetic fragrances. Following Perkin's discovery and commercialisation of mauvine in the 1850s, the world's first synthetic dye, chemists were searching for non-natural organic molecules with financial value. In the days before structural determination and enzyme assays, only very few useful properties were evident. Colour and smell were obvious, however, quickly leading to many new dyes and perfumery compounds. Whilst at first largely hit and miss, some general structure-smell relations are now known, for instance salicylates, closely related to aspirin, can be synthesised to give orchid-like smells.

Aromatic substances used in perfumery are largely plant derived and extracted through various means such as destructive distillation or solvent extraction, often using petrol. There are examples of all parts of

Perfume bottles often cost more to produce than their contents

the plant being commercially used, from anise seeds, cinnamon bark, juniper berries and myrrh resin, to name but a few. Chemically, the extracts may be pure or complex mixtures, and run the gamut of all major classes of secondary metabolites, including terpenes, polyketides, glycosides, alkaloids and fatty acid derived molecules. For example, many pine and other wood essential oils are formed of the same terpenes in differing quantities, leading to different smells.

In the past, animal substances were more widely used than today. Beavers, whose testicles were one source of musk, were believed in the middle ages to bite off the organs in question and show them to the hunter when pursued. This would deem them worthless and their life would be spared. This belief was still sufficiently prevalent for Thomas Browne to feel the need to dispel it in his 1646 book, *Vulgar Errors.*

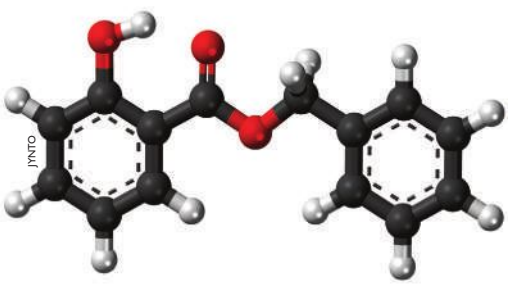
Have you ever noticed how after experiencing a smell for a while, the intensity seems to drop or disappear entirely? Well, perfumers have the solution, which is termed 'notes'. After application of the scent, the most potent smells arise from the most volatile compounds, being the most easily evaporated. As these compounds become reduced in concentration on the skin, the next most volatile compounds become the dominant smell, as they are still present in large quantities, and so on. The series of layers of smells that are achieved are called top notes, coming first, mid notes following those and finally low or base notes. This allows the wearer to achieve a changing fragrance, which is more noticeable to those around them.

So I can make my perfect perfume just by finding a top, a middle and a bass note I like and then mix them together, right? Well, before you all rush to your stills, you must consider that the mixture of liquids will affect the volatility of its parts. So when a bass note is added to a top note, the top note may become more or less volatile, making it either shorter or longer lived. Theory is pretty fallible in predicting even simple systems. Move to multi-component ones and all you can do is mix them and see. This is just one of the ways in which perfumery has an inevitable artistry to it.

Many organic chemists claim to be able to tell certain functional groups by smell alone. If the lab smells fishy, someone has probably been using an amine. Also, it is well known that hydrogen cyanide smells like almonds, which having worked with it, I can confirm. Interestingly, if you are extremely paranoid about being poisoned by cyanide, you can improvise your own antidote, as the legal recreational drug poppers is principally amyl nitrite, the antidote to cyanide poisoning. However, due to health risks, this is probably not advisable.

The chemical responsible for the natural smell of almonds is benzaldehyde. It has been suggested that the cause of the similarity in the smell with hydrogen cyanide is due to both molecules stimulating the same olfactory receptor, something that they can do due to having similar vibrational frequencies when bound to the protein. In some sense, we, when smelling, may be 'listening' to the scent molecules. This vibrational theory of smell is not completely accepted, and an alternative weak-shape theory has also been proposed, which is that only small regions of molecules are bound strongly and therefore 'identified' by a receptor. This would explain how chemists can smell functional groups, if not why cyanide smells like almonds.

Scientists also don't fully understand why perfumes cost so much. For example, sales of Justin Bieber's line of fragrances were $37,000,000 in 2013. And what does the liquid in the bottle cost to produce? Well, obviously this is a little hard to find out, but marketing research groups estimated that in a typical $100 perfume, the smelly stuff only sets the manufacturer back $2, less than half the cost of the bottle. β



Benzyl salicylate, like many esters, has a pleasant smell often used in perfumes

Rob Scanes is a 4th year undergraduate in the Department of Chemistry.

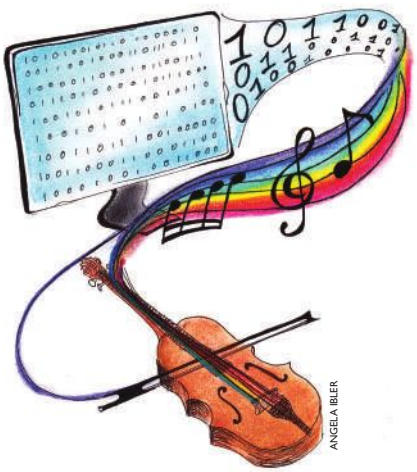
Rhythm and Algorithm

Robin Lamboll reveals how computers can make music

CAN COMPUTERS CREATE MUSIC? Music is a highly mathematical artform that relies on many symmetries and relationships between notes to create pleasing harmonies. If computers can do maths faster than humans, why not make music too?

In fact, algorithms for writing music considerably predate the electric computer. In the Renaissance and Baroque period, a highly rule-based style of two-voiced music known as counterpoint was in fashion. Following all the rules of the genre meant that at any point, there were only a limited number of options to pick. In the 1700s, this resulted in the publishing of several 'musical dice games'. Merely by rolling a die or two and looking up rules on a table, people could put in order some bars of pre-composed music in ways that followed the musical conventions. Many different versions of the game - often attributed to Mozart, Hayden or other great composers - still exist. Although this attribution is uncertain, it seems that Mozart wrote some numbered two-bar snatches that have been used in a game like this. However, we have little difficulty here in assigning the musical skill involved to those composers, rather than the person rolling the die.

Since the 1950s, musicians have been able to use computers to follow the algorithms. The Illiac Suite, by Hiller and Isaacson of the University of Illanois in 1957, was the first computer-generated musical score. Although the algorithm relied heavily on random numbers, it never used pre-written bars of music. The first few bars consist of notes generated randomly, then additional rules were slowly imposed until the last few bars were written in full counterpoint. Later algorithms have become more sophisticated, either being based on more general rules for making music or, more intriguingly, combing existing musical works for what makes them work. There have been several attempts to make music based purely on mathematical relations, such as using inputs like the structures of proteins. Here, multiple levels of information, from the individual building blocks of the protein to large-range structure, can be encoded in notes, durations and harmonies. However, it's fair to say that these musical pieces lack the themes and structures that keep music engaging.



Some computer compositions can easily pass for human music

The computer program 'Experiments in Musical Intelligence' (EMI), written by composer David Cope, is trained to replicate the feel of different classical and jazz composers by analysing their works in detail. It has been reasonably successful in creating music that can pass blind tests, sometimes being preferred by audiences to the works of real human composers. As well as creating works in the style of classical composers and Cope himself, Cope has programmed EMI to write music in the style of an entirely new composer he has named Emily Howell. Whilst not necessarily masterpieces, her compositions can easily pass as human music.

There are also some more unusual approaches to music via genetic algorithms. These are a family of computer codes that take a basic input, alter (or mutate) it in different ways and then compares the different new versions. This approach is used to solve mathematical problems. However, if we have a mathematical description of what makes good music, we can also make random sounds evolve into something beautiful. By using related families of music, we can have motifs and themes, like in most great works. The core problem is then simply working out what beauty is, mathematically. Whilst there are some easily-encoded choices such as avoiding unpleasant combinations of notes, mostly it seems quite complicated and therefore difficult to write. As of yet, most successful music generation programmes have therefore been based on the idea of generating lots of music, and humans select what works. For the moment then, machines still need us to teach them true beauty. But for how long?

Robin Lamboll is a PhD student in the Department of Physics.

Plant to Power

Shobana Sivanendran and Oliver Caspari investigate the Plant to Power project.

If you've recently entered the Botanic Gardens from Hills Road, you will probably have noticed a timber structure covered in plants and a few striking translucent orange panels. This is the Plant to Power (P2P) project, the brainchild of Dr Paolo Bombelli and Prof Chris Howe from the Department of Biochemistry at the University of Cambridge. What might originally seem like a creative concept for façade design is actually a brilliant idea to harness electricity from plants. The biologically generated electricity will be supplemented by solar power harvested from the orange panels. This project combines three main concepts – a living wall, a plant bioelectrochemical system (BES) and a solar power generation system

Using microbes to generate electricity was first discovered by Prof Michael Cressé Potter over a century ago in Durham. Like all cells, microbes metabolise nutrients to generate energy. In this process, electrons are usually transferred onto oxygen, producing CO_2 and water. However, when oxygen levels are low, like in most soils, organisms need to find other ways to dispose of these electrons. In P2P, microbes feed on nutrients released from plant roots in the soil. The microbes transfer the electrons produced from burning these nutrients onto an electrode, generating a current in the plant-BES.

Currently, the amount of power generated is very low. For example, covering King's College Chapel entirely with living walls would generate just enough electricity to power a laptop. However, if you are growing plants anyway, plant-BES allows power to be generated simultaneously. Thus, fitting agricultural fields with electrodes could be a great way of diversifying the green energy portfolio in the UK, but may have an even bigger impact in places that are off the power grid. Equally, if you are fitting a living wall to your house for insulation or to start your urban vegetable patch, why not get some electricity out on top of fresh tomatoes?

In the long term, the team in Cambridge are pushing for higher efficiencies to allow the technology to be a viable alternative in the spectrum of green energies, which would require least 1 Watt/metre^2. Paolo Bombelli believes that using photosynthetic algae and cyanobacteria may pave the way. Connected to an electrode, these organisms can directly provide electrons extracted from water photosynthetically. Such 'biophotovoltaic devices' have already achieved power output comparable to biofuels whilst needing less fossil fuel input to grow and distribute the energy. Because the cells continue to generate electrons from burning nutrients, like in the plant-BES, power generation continues throughout the night, unlike solar cells.

The P2P project is a demonstration of proof of concept rather than a potential commercial application. However, the fact that electricity can be generated from widely-available, existing photosysthetic systems is incredibly exciting from a green energy perspective. Whilst still in its infancy, this idea of power generation from microbes has many promising applications in a future increasingly constrained by depleting non-renewable energy resources. Chris Howe believes that "electrical generation in cyanobacteria is going to be a very interesting research area in the future."

The team's next project in the London Zoo is another big step in this direction. Multiple panels of moss will generate electricity in a similar manner to the plant-BES system in the P2P project. This energy will power a camera that will capture images of wildlife that lives in the vicinity. It is an exploration of the idea of generating electricity from existing forests and jungles to collect information on endemic wildlife. It will be open to the public in the autumn, and shall remain so for approximately six months. So do drop by if you are in the area! β

Solar panels and plants working together in the botanical gardens

Shobana Sivanendran is a PhD student in the Department of Engineering and Oliver Caspari is a 4th year PhD student in the Department of Plant Sciences.

(Wo)mentoring

Amy Danson talks to Prof Dame Athene Donald and Prof Tim Bussey about the importance of female role models and mentors in science

Prof Dame Athene Donald

WOMEN IN EUROPE are extremely lucky; we can vote, express our views freely, we have access to education and we can work. Relatively speaking, things are pretty great for females. But gender equality in the UK is far from perfect and in no field is it a more controversial topic than in science. Whether you blame childbearing, a lack of 'leadership qualities' or some other unconvincing biological asymmetry for the so-called leaky pipeline effect, there's no doubt that whilst many women embark on an academic career in science, few make it to the top. In fact, just 20% of professors in the UK are women. What's more, our fledgling, could-be scientists are bombarded with gender stereotypes from their first breaths. The myth that boys are better than girls at maths and science still pollutes schools, even in 2015. How do we combat the negative impact of these falsehoods and preconceptions? I spoke to Prof Dame Athene Donald, professor of Experimental Physics and the 2009 International Women in Science Laureate, and Prof Tim Bussey, behavioural neuroscientist and ScienceGrrl team collaborator, about what I consider to be one of the most important and positive solutions: female role models, including mentors and sponsors.

Athene recently published an article in *The Guardian* in response to the frenzy surrounding Tim Hunt's comments on women in the lab. In it, she challenges the reader to commit to "just one action for women in science" (#just1action4WIS). She outlines a number of action points that she suggests could actively help the cause, instead of merely joining the Twitter 'lynch mob', as millions of people did. One of her key pieces of advice is to "act as a sponsor or mentor". I asked her to explain the difference between these two roles.

"I think most people know what mentors are; they are someone that you can go to for advice," said Athene. "But I think in many cases the best mentors are the ones that you come across at a conference or in the tea room, and you find someone you can relate to and feel confident saying 'I'm not confident' to, because it takes quite a lot of courage to say 'I don't know what I'm doing'!"

She says, however, that 'sponsor' is a relatively new term, and one that she hadn't come across until she read a book called 'Forget a Mentor: Find a Sponsor' by Sylvia Ann Hewlett. "The idea is that people who may be relatively senior look out for people that they think were really good in a talk... since there is a lot of fuss about conferences having no female speakers, it is particularly important, but it may also be about jobs," Athene said. A sponsor is someone who would either recommend you for a position or would encourage you to apply for a position – something that a mentor with whom you have a more informal relationship might not do. Although she's not convinced that she herself had a female mentor who particularly influenced her career path, she does mention that Sir Sam Edwards, head of the Physics department and Cavendish Professor of Physics during Athene's time, probably acted as her sponsor and was "incredibly important" in leading her to where she is now. In particular, he gave her the advice that "intelligent women should have families".

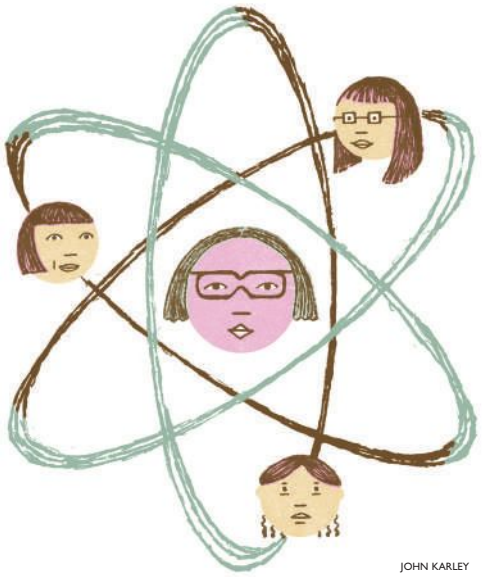
Prof Bussey, by contrast, has had many female role models; from his mother, who worked in a pathology lab, to his wife Dr Lisa Saksida, with whom he shares his lab in the department of Psychology. He suspects that these women, as well as his undergraduate supervisor Dr Emma Wood and his post-doctoral supervisor Dr Betsy Murray, were the inspiration for his involvement in the ScienceGrrl movement, along with his band Violet Transmissions. ScienceGrrl are a network of scientists, dedicated to celebrating and supporting women in science and passing on their passion to the next generation. Now a veritable YouTube sensation and a highlight of Pembroke College May Ball this year, Prof Bussey's band have been promoting ScienceGrrl's message and

Prof Bussey and his band *Violet Transmissions* cover Thomas Dolby 's 1982 hit 'She Blinded Me with Science' at Pembroke College May Ball

recommendations with their cover of Thomas Dolby's 1982 hit song 'She Blinded Me With Science'. When I asked Prof Tim Bussey about whether he in turn had acted as a mentor or a sponsor for the women in his lab, he said he had never really thought that they were different: "You do mentor people with respect to what they're doing at the time but there's no question that when they move on you are their 'advocate'. For me it happens naturally because you want people to do well," although he admits that he is well aware of principal investigators that don't support their ex-members.

At least anecdotally, mentors and sponsors are valuable for women and men alike, throughout their careers. But what about at school? A Wellcome Trust report in 2013 found that "young women are more likely to be concerned about science not being a field for 'people like me' than young men are". I asked Athene whether schools went far enough to expose young people to female role models in science and engineering. "No, absolutely not," she replied. "I think that schools are certainly part of the problem in a sort of benign, neglect kind of way. I am appalled when I talk to a general audience about women in science and someone says 'well my 11 year old niece was told that maths wasn't for girls'." She says schemes like the 'Inspiring Women Network', set up by Miriam González Durántez, in which women from all different career types go into schools and talk to young people about their job opportunities, are a very positive thing. In addition, other schemes that aim to engage younger children with science, like the Cambridge Hands on Science (CHaOS) team, are critical in the battle against gender inequality in science. Showcasing female role models during these early years can only serve to raise girls' confidence, and their families' and teachers' expectations.

So you're probably reading this and thinking that female role models and mentors are a great idea, but how do you go about becoming one? Athene talks about a workshop that was run by the university for the Senior Gender Equality Network: "One senior female administrator said 'I'd never thought of myself as a role model for those behind me' Just talking about what she could bring and what was needed brought that out... I'm sure she did talk to younger women but she hadn't quite formalised it in her head. I think that was a very useful thing and for the men too." Being a role model seems to be more than giving advice to your juniors – it's about being proof that the next step or even the final step in a career progression is possible for a woman. It's about encouragement and an attitude that says 'if I can do it then so can you'. The words 'role model' might conjure up an image of a person blessed with success and confidence, with integrity and a good reputation, whilst in reality, anyone can act as one. Why not make a list of your experiences and qualities that you think would help or inspire someone, and then work out how you could use them? Make it your #just1action4WIS.



JOHN KARLEY

Showcasing female role models during early years can only serve to raise girls' confidence, and their families' and teachers' expectations

Amy Danson is a 4th year undergraduate in the Department of Biochemistry.

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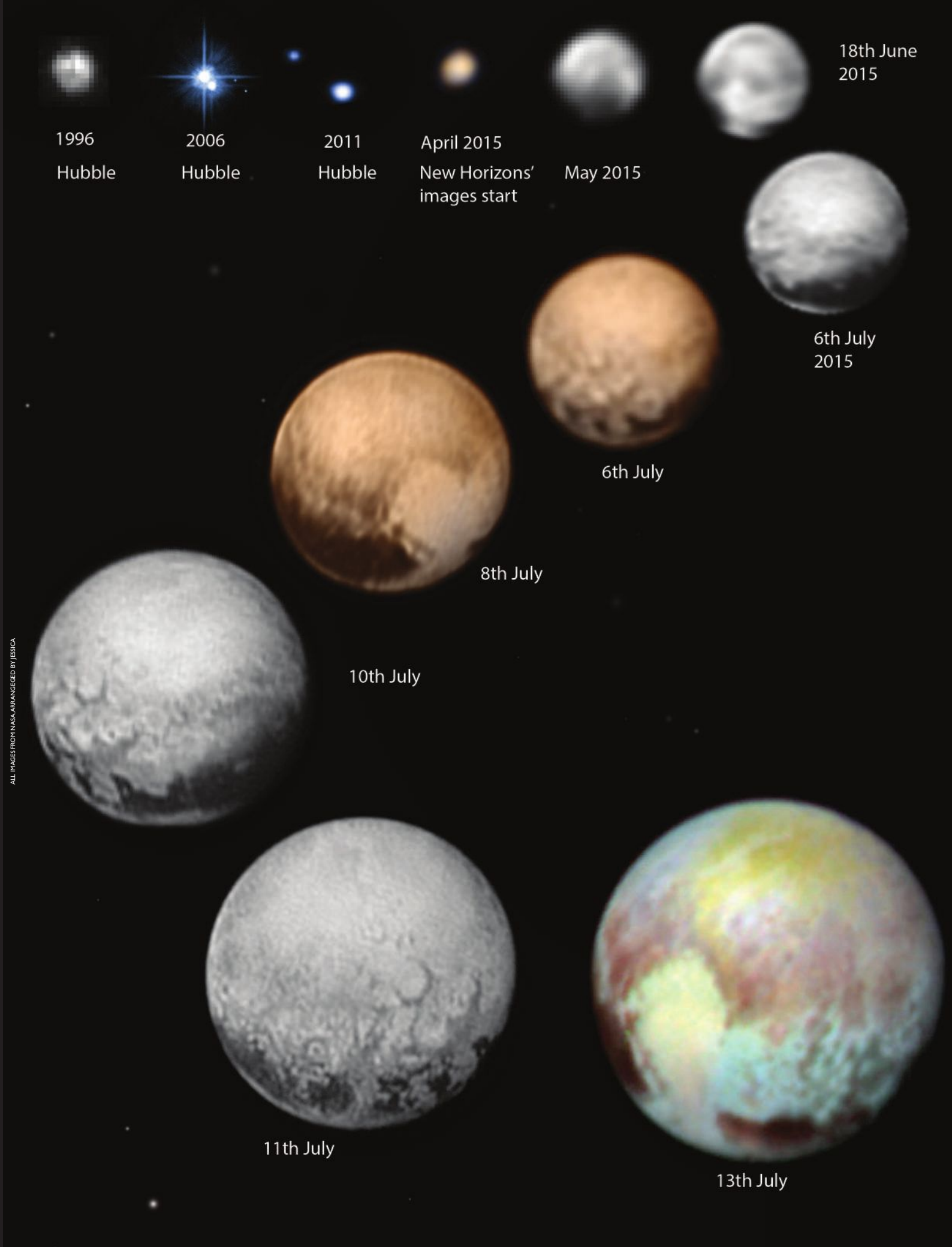
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Hubble
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New Horizons' images start
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ALL IMAGES FROM NASA ARRANGEGED BY JESSICA

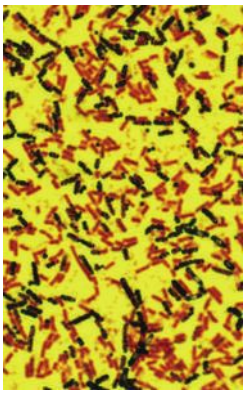
New Horizons on Pluto

NASA's 'New Horizons' probe has finally made its closest approach to Pluto! Making the 5 billion kilometer journey in just less than 10 years, it's the fastest space journey ever made. With six different spectrometers looking at a range of visible and invisible light, it will take months to send back all its data over such vast distances, but we've already received enough for several revelations. First, we've confirmed that Pluto is the largest known dwarf planet in the solar system. We've seen from the large, crater-free areas that it has geological activity. We've revealed the extent of its nitrogen atmosphere, and solar wind measurements show that it's being ionised and blasted away into space, losing gas at rates of hundreds of tons per hour. Keep an eye out for more discoveries! RL

14th July, 2015
New Horizons' closest approach

Overcoming the 'Great Plate Count Anomaly'

Jenni Westoby describes an innovative new way to culture interesting bacteria.



JOSEF REISCHIG

Only one percent of all known bacteria can be grown on Petri dishes

THE HUMBLE PETRI DISH can be found in many places, from teaching laboratories in schools to top research labs in Cambridge. Yet, one of the main functions of the Petri dish may be about to be surpassed by a new, more successful technology. A team at Northeastern University in Massachusetts, has developed a low-tech solution to a long-standing problem in microbiology. The iChip is a thumb-sized plastic chip that could spell the end of the Petri dish's monopoly in microbiology.

So what can the iChip do that the Petri dish can't? Well, for a start, bacteria actually grow on it. Plating bacteria on a Petri dish, a small, round container made of plastic or glass, has been the main way of growing bacteria in a lab for over a century. But only one percent of all known bacteria can be grown in a lab on Petri dishes. The reasons behind this huge discrepancy in number remain a mystery: the 'Great Plate Count Anomaly'.

Unfortunately, the fact that we have been able to study only a fraction of all bacteria is not trivial. Bacteria have been the source of some of our most important medical discoveries, including the most common antibiotics. As more and more bacteria evolve resistance to existing antibiotics, it is becoming increasingly important that we find ways to grow the remaining 99 percent of bacteria in the hope of isolating new antibiotics from them.

Scientists suspect that there are two main reasons many species of bacteria struggle to grow on Petri dishes in the lab. First, we are starting to realise that the growth medium used in Petri dishes, such as agar gel, may produce chemicals that are toxic to many bacteria. In the December 2014 issue of Applied and Environmental Microbiology, a group at Japan's National Institute of Advanced and Industrial Science and Technology published some surprising findings: bacteria grow more readily on Petri dishes if the agar gel growth medium is produced in a different way.

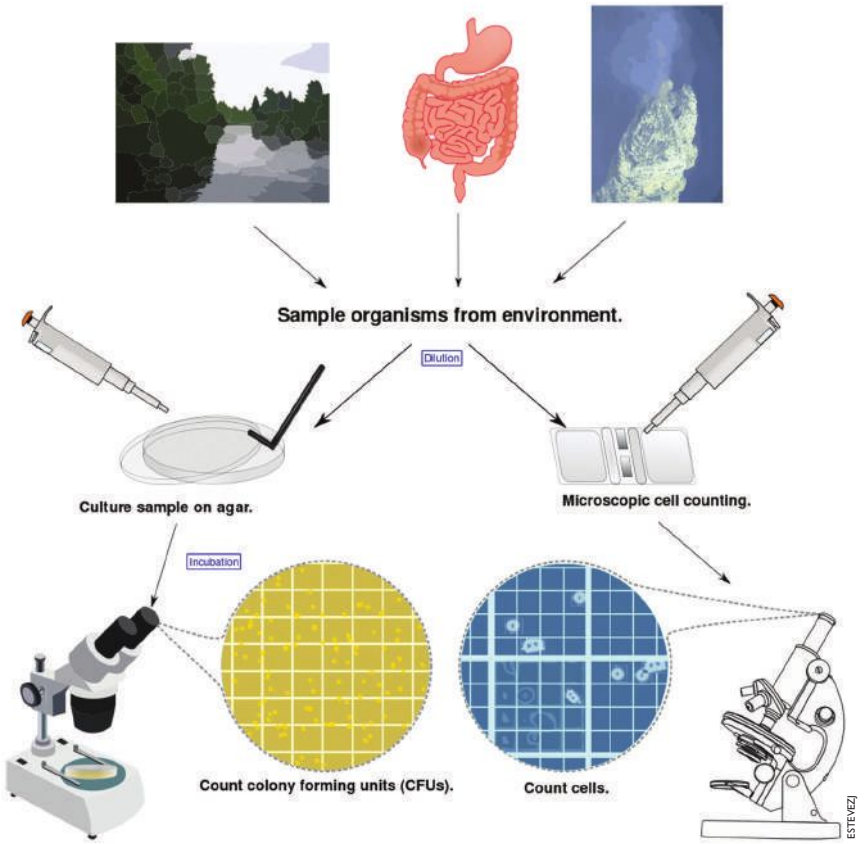
ROBYN CARTWRIGHT

The iChip is a plastic chip full of chambers for growing bacteria for drug discovery

Traditionally, agar gel is prepared by mixing phosphate with agar, a gelling agent obtained from algae. This mixture is then subjected to high-pressure steam, a process known as autoclaving. However, when the Japanese researchers tried autoclaving the phosphate and agar separately prior to mixing them, or not adding phosphate at all, they were able to grow more bacteria on these Petri dishes than normal. It appears that the concentration of hydrogen peroxide, which is produced during autoclaving, increases as the concentration of phosphate grows. The authors suggest that the production of hydrogen peroxide and other reactive substances, which is a direct result of autoclaving agar and phosphate together, may be the reason that most bacteria can't grow on Petri dishes. This suggests that the plate count anomaly could be partly overcome by changing the way we produce agar gel.

But this is only a partial answer. Many bacteria appear to require complex mixtures of nutrients and chemicals to grow well. These substances, which bacteria normally receive from the environment, may not be present in the growth medium used in Petri dishes. Additionally, toxic waste products produced by the bacteria may build up to a level that can kill them in a sealed Petri dish.

This is where the iChip comes in. A portmanteau of isolation and chip, the iChip is a plastic plate, honeycombed with 384 pinhole 'diffusion chambers'. It allows bacteria to be grown *in situ*—or in their natural environment—and subsequently studied in the lab. The walls of the diffusion chambers are permeable, allowing small molecules such as nutrients needed for growth to enter and gases, nutrients, and the cell's waste products to leave the chamber. By cultivating bacteria in their natural habitat, scientists can study more bacteria than ever before.



The iChip has opened up a new world of bacteria that we were previously unable to study

In a 2010 paper in *Applied and Environmental Microbiology*, Nichols *et al.* ran a series of experiments in which they grew soil and seawater bacteria in both Petri dishes and iChips. When the results were compared, they found that the fraction of bacteria able to grow in the iChip was fivefold higher than the Petri dish. The bacteria grown in the iChip were also more likely to be bacteria that had never been cultivated before.

The success of the iChip is demonstrated by the fact that the first member of a new class of antibiotic substance has already been discovered using it. In a January 2015 Nature paper, Ling *et al.* used the iChip to cultivate bacteria *in situ*. They then screened extracts from the isolated bacteria for antibiotic properties. Teixobactin, a chemical compound produced by a newly identified species of bacteria provisionally called *Eleftheriaterrae*, was found to be effective against a wide range of disease-causing bacteria, including some extremely drug-resistant strains like methicillin-resistant *Staphylococcus aureus* (MRSA). Even though Teixobactin can't solve the antibiotic resistance crisis alone, and further research needs to be done before Teixobactin can be prescribed to humans, it is a very promising discovery. The iChip has opened up a new world of bacteria that we were previously unable to study, and new antibiotics come as part of the package.

So has the iChip made the Petri dish redundant? Not entirely. Lots of organisms in addition to bacteria are grown on Petri dishes, and it is possible that by continuing to tinker with the way we make growth media, the great plate count anomaly could be gradually reduced. Some bacteria that grow on Petri dishes don't grow on the iChip, meaning for studies on certain bacteria the Petri dish may remain the only choice.

Nevertheless, the iChip clearly represents a huge breakthrough in microbiology. Previously, cultivating bacteria in diffusion chambers was laborious and time-consuming. The iChip has made this process relatively quick and easy by allowing high-throughput cultivation in hundreds of tiny diffusion chambers. Not only does the iChip allow much more rapid cultivation of bacteria, it also gives us the opportunity to study many previously 'uncultivate-able'bacterial species for the first time. The iChip has opened up a vast untapped biomolecular resource of new potential antibiotics and medicines. With an antibiotic resistance crisis looming, this technology couldn't have come at a better time.

Jenni Westoby is an undergraduate student at Sidney Sussex College.

Weird and Wonderful

A selection of the wackiest research in the world of science

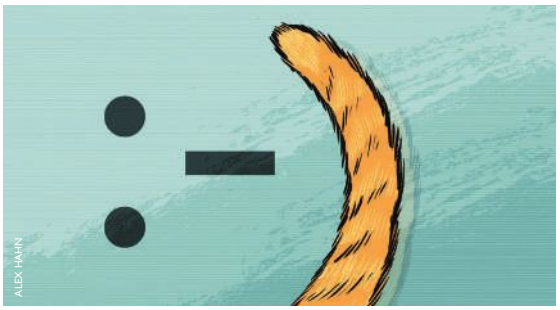
The Bra That Can Save Your Life

IN CASE OF AN EMERGENCY, such as a fire, inhalation of toxic particles can be reduced by wearing a simple protective face mask. But how many of us carry one around, just in case? Dr. Elena Bodnar thinks we should. This doctor of medicine treated children affected by the Chernobyl nuclear accident, and her work inspired her to invent the Emergency Bra: a bra that can be quickly converted into two protective masks. Not to worry – no stripping is required. The Emergency Bra can be removed while keeping clothes on. This versatile invention, which is now commercially available, earned Bodnar the 2009 Ig Nobel Prize in Public Health. According to her website, the benefits of having one at hand are numerous. As well as reducing inhalation of harmful particles, it straps securely round the back of your head, freeing your hands to keep balance and remove any obstacles. It may also reduce the chance of panic attacks because it gives the wearer a sense of security. You may now be thinking: but any face mask can do all that! Well, yes. But do they also come in an attractive range of colours and guarantee a great cleavage? I don't think so. **AD**

Laser Ravens to Save a Tortoise

TORTOISES ACROSS THE WORLD face many threats, from changing habitats to motor vehicles, but young desert tortoises are particularly vulnerable to attacks by ravens. To protect the babies, environmentalists have started shooting the ravens – not with bullets, but with lasers. Since humans began bringing rubbish and shade into the Mojave Desert in California, the raven population has multiplied by a factor of 15 in three decades. This means that when baby desert tortoises are born, they can quickly be snapped up by the waiting ravens. As a result of this, the tortoises are now listed as vulnerable to extinction. However, environmentalists led by Tim Shields have banded together to chase the ravens away by firing weak lasers into the ravens' eyes. This does not lead to any lasting damage, instead it unsettles the birds and teaches them to stay away from tortoise hatching areas, giving the young a chance at life. Currently, people located on site fire the lasers, but Hardshell Labs are developing computer games so that people throughout the world can operate automated lasers or similar devices to repel invasive or overnumerous species. Environmentally friendly laser tag, anyone? **RL**

The Internet is Made of Cats



WITH OVER 26 BILLION views of more than 2 million cat videos on YouTube, there are an awful lot of cats on the internet. Why are we so obsessed with feline frolics? Why do 50 per cent of people who watch internet cats feel the need to 'share' the moggy love on social media?
In a recent Computers in Human Behaviour publication, Jessica Gall Myrick explored the emotional effects caused by internet cat viewing. She found in a survey with almost 7000 respondents that most people don't intend to watch cats on the internet, but when they do, 75 percent 'like' it in some fashion and feel more positive emotions afterwards, suggesting a potential for online pet therapy in the future. Motivations behind watching cat videos could affect mood too – procrastination was found to be a major predictor of guilt. Interestingly, feelings of guilt did not increase overall negative emotions if the subject enjoyed the kitty content. So what do we make of all this? Well, that it's OK to look at LOLcats when you should be studying, as long as you enjoy it!

'Some people think the internet… is made of wires, lasers and some hats… but they're all wrong because the internet is made of cats!'
rathergood.com
EW

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