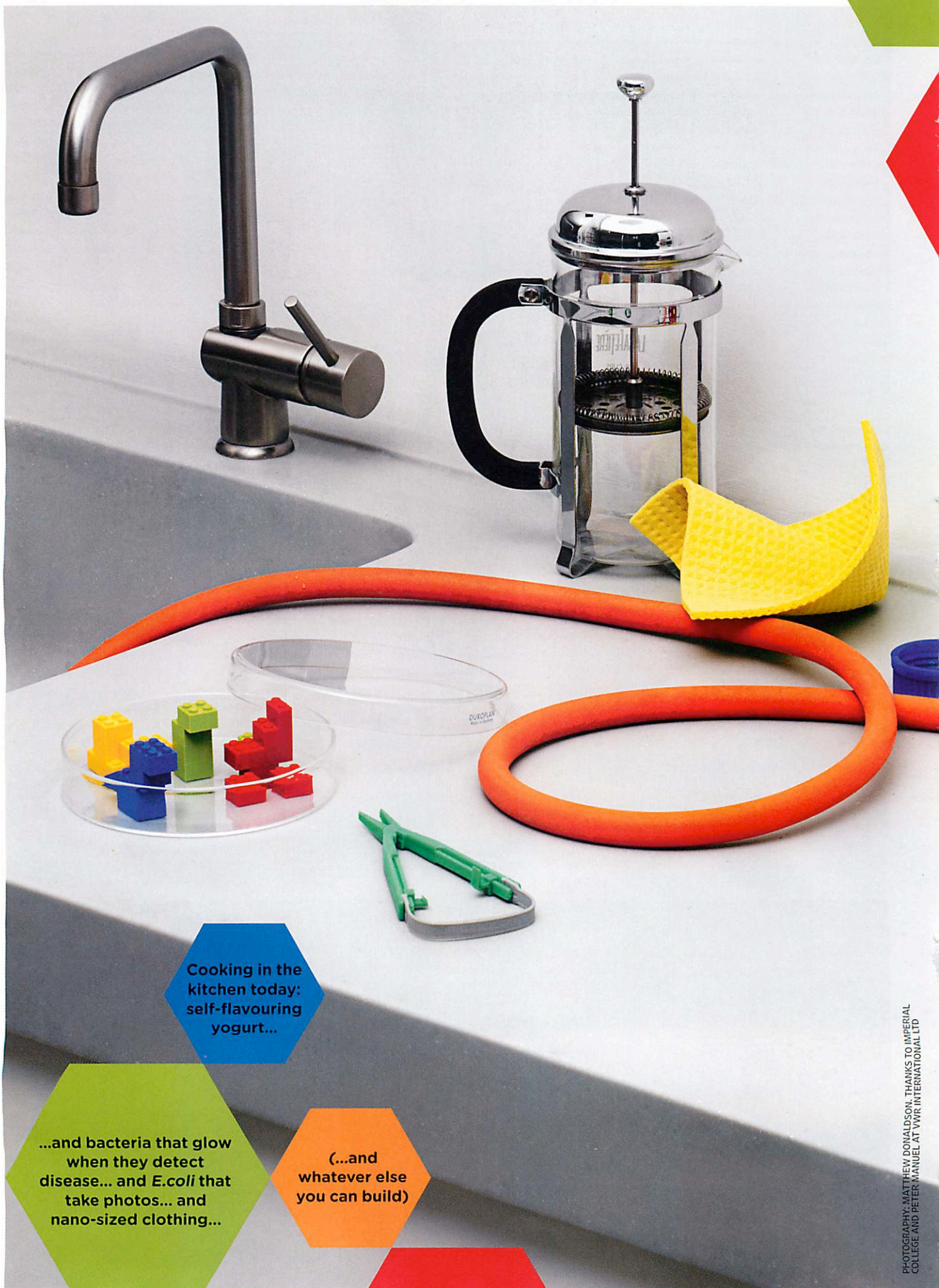

PHOTOGRAPHY: MATTHEW DONALDSON. THANKS TO IMPERIAL COLLEGE AND PETER MANUEL AT VWR INTERNATIONAL LTD

At home with the DNA hackers

Words
Ben
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Scientists are manipulating genetic material to **create new forms of life.** 'Synthetic biology' is causing a buzz. But what of the risks?

Portraits
Jason Joyce
Jason Grow

Still life
Matthew
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TOM KNIGHT, OFTEN CALLED THE "FATHER" OF BIOHACKING, TELLS A JOKE: "A biologist goes into the lab one day, does an experiment and finds something is twice as complicated as she thought it was. **'Great,'** she says, 'I get to write a paper.' An engineer goes into another lab, does an experiment, and she too finds something twice as complicated as she was expecting. **'Damn,' she says, 'Now how do I get rid of that?'"**

It's a modest joke, but one that shows the clash of philosophies that has led to the birth of a new science. This emerging field promises innovations ranging from better computers to limitless fuel to new medicine. Even as you read this, its vast possibilities are driving a thousand students from around the world into a competition not just to invent a product or some computer code, but to develop whole new forms of life, specially made to work for us.

Welcome to synthetic biology.

Tom Knight is a computer scientist by training – a legendary one at that, having attended MIT at 14 – and a pioneer of processor design and networking systems since the mid-60s. He decided in 1990 or so "that the hot new area for technologists was going to be based not on physics, but on biology." His hunch sent him back to the MIT lecture halls, where he become a grad student in biology.

But in 1996 he set up his own lab, and he's been "going at it from an engineering point of view since then". This was because the process of learning biology left Knight frustrated. For one thing, the methods of making DNA were maddeningly imprecise. "The way in which these experiments got done always required a careful and detailed understanding of what was happening," he recalls. "Every time you wanted to do an experiment with DNA it became two experiments: the one you had in mind, and the one where you made that piece of DNA." The learning process also offended his engineering sensibilities: "The way it's done right now looks something like a medieval craft. It's very much like an apprenticeship system from the Middle Ages. Find the master, study at the feet of the master... That's very different to the way an engineer gets things done."

The scientist's job, Knight believes, "is to understand nature however it occurs and in all its wonderful complexity. But the complexity of the biological world does not inspire me: it's an impediment in most cases. My focus has always been on the creation of an engineering discipline. I want to create systems that are still alive, but are more simple and more understandable."

His aim was to take the wet, complicated, messy business of life – DNA, proteins, cell biology – and abstract them into systems. And then to use that knowledge to build new and useful organisms.

His solution: standardised parts.

Let's go with a historical analogy, and introduce Henry Maudslay – a curious man, perhaps, to whom to attribute a key idea of synthetic biology. For one thing, he trained as a blacksmith; and he did his pertinent work in 1799. A master craftsman by 18, Maudslay was working for the industrial pioneer Joseph Bramah when he invented the slide-rest lathe. A lathe is a machine on which the workman holds a blade against a spinning piece of wood or metal to shape it. It's how table legs or metal rods can be fashioned, but at the time it was inaccurate work: the operator would hold the blade in his hand and estimate by sight how much needed to be cut – how much pressure to apply, and for how long. Maudslay mounted the cutting blades in vices that could be slid left and right, in and out, so that each new piece could be cut accurately and, most importantly, identically to the last one.

By 1797, Maudslay's genius meant he'd been made Bramah's workshop manager and married his boss's housemaid. With four children and a growing reputation, Maudslay did the natural thing and asked for a raise. Refused, he did what his entrepreneurial engineering successors have done ever since, from London to Silicon Valley: he left for his own start-up.

And so, in a workshop just off Oxford Street in central London, he made his breakthrough. Building on his slide-rest lathe, Maudslay created a machine that could cut screws to standard sizes: quickly, accurately and in bulk. This was new. Previously, mechanical engineers had to cut each screw, nut and bolt individually. Nuts and bolts were especially tricky: they had to be made in pairs and losing one rendered the other useless. The

PHOTOGRAPHY: JASON JOYCE

HOW A BIOHACKER PLAYS WITH LIFE

Step 1

Order some *E.coli* (you'll need official accreditation), a strain bred to be safe and usable in the lab. The most popular is bred from "K-12" – found in 1922 in a Californian diphtheria patient.

Step 2

Then make the *E.coli* "competent", that is, ready to take up and incorporate foreign DNA. You'd do this with TSS buffer: the recipe is on *openwetware.org*

Step 3

With your *E.coli* prepped and in a test tube, add the DNA and mix well. Sit this mixture in an ice bath for 30 minutes, then warm your test tube in water at 42°C for 30 seconds.

Step 4

To your new mixture, add some SOC medium – the sugary soup that bacteria like to live in (recipes are online) – and warm the mixture for an hour at 37°C.

Step 5

Empty the test tube into *a petri dish* filled with bacteria food, such as the tasty LB medium, and incubate your new creature *overnight in a* warm place. Now wash your hands.

individual machining of bespoke bolts was laborious, inaccurate work; now, not only were nuts and bolts interchangeable, but they were cheap. For the first time, you could buy a bag of them all the same size.

Just as the industrial revolution was beginning, Maudslay's tool meant that engineers could stop worrying about manufacturing the nuts and bolts and get on with thinking about the wider system. Not having to worry about *how* things join together would let creators dream instead of what might happen when they do.

Why not take the same approach to genetics? Biology, Tom Knight saw, had to be made more like engineering. He developed a system whereby individual chunks of DNA known to have specific effects – to cause a cell to glow, say, or to smell of bananas, or to produce a protein that reacts in a particular way – could be separated out and made in bulk. These parts, which he called BioBricks, have standardised means of being manufactured and of being used. Genetic engineering could start to look like mechanical engineering.

"An advantage of making standardised parts," says Knight, "is that you can become really good at it."

It's an approach that is not without its detractors within the field of biology. As Knight puts it: "They say, 'You take two pieces of DNA, you put them together, who knows what you get? It's a complicated system!' But the whole *idea* is to be able to compose parts where the functional result is what you wanted. There may be other things happening, but that's not what we're interested in. We want to make intentionally simplified and [he stresses] *wrong* models."

You can see what he means by looking at the Registry of Standard Biological Parts at *partsregistry.org*. This website, founded by Knight and his students, holds the details of more than 3,000 BioBricks, with parts listed by function: parts that produce smells, parts that cause cells to move, parts that let cells "talk" to their neighbours. Dig deep enough and you can, if you wish, find the transcript of the DNA and the underlying biology, but that's not the point. It would be like knowing the ingredients of the plastic that makes up your Lego bricks: the whole point is to be able to build stuff from parts by knowing *what* they do, not *how* they do it.

'Synthetic biology is just on the precipice of becoming a **whole order of magnitude easier'**
Jim Haseloff

Jim Haseloff in his Cambridge lab, in the university's plant sciences department

And build stuff you can. The International Genetically Engineered Machine (iGEM) competition runs every summer for undergrads the world over to produce the most impressive works of synthetic biology. The teams are partly biologists, partly engineers.

"Most teams are half-and-half," says Vincent Rouilly, an iGEM instructor from Imperial College, London. Rouilly was a software engineer before he was a synthetic biologist. "It's interesting when you have two cultures, trying to build something in common, where they don't have the same way of thinking," he says. "The mindset is quite different when you come from a life-sciences to an engineering background."

The 120 teams, eight from the UK,

will present their projects at the next iGEM jamboree at MIT in November. They'll get support from companies like the one recently cofounded by Tom Knight, Ginkgo Bioworks – one of many start-ups emerging to seek to profit from the new field.

"One, we're trying to make it easier to 'snap' parts together and, two, we're trying to make better parts," says another Ginkgo cofounder, Reshma Shetty. She's become famous for demonstrations at geek conferences. At this year's Foo Camp in California, for example, Ginkgo helped participants engineer colonies of bacteria to smell of banana, or glow in the dark, or turn red.

So how does this actually work? According to Shetty, the individual parts – which, remember, are just specific strips of DNA – are typically stained with food colouring and then allowed to dry out. They ship in little swatches, like watercolours. All you need to do is add water, take a pipette, and drip the new DNA over some bacteria previously prepared to be ready to accept it. You can, if you're from an accredited academic institution, order such bacteria online, and it will arrive in the post. Lab-grade *E.coli* is the most popular, specially made to be safe to use. Nurture the *E.coli* at the right temperature overnight, and in the morning it will have taken up the DNA to do what you want.

As simple as this sounds, it still takes time. Too much time, says Shetty: "It might take a week to design a part, a few weeks to get the DNA back from the synthesis company, a week to test the part... If it takes a month to go all the way around the loop, how long will a ten-part system take?"

That's what Ginkgo and others are trying to solve. By standardising parts and increasing the speed at which you can synthesise DNA, you can try many variations. Synthetic biology potentially allows for scores of prototypes to be grown overnight at once. "It's just on the precipice of becoming a whole order of magnitude easier," says Jim Haseloff of the University of Cambridge, a pioneer in the field of plant genetics. "The iGEM competitors will then have access to 'megabase' DNA sequencers and take a design that today would cost millions of pounds – and have it happen overnight for no money." (Megabase DNA sequencers can produce very long strands of DNA in one go. Each strand can be thousands of pairs in length.)

"It's not quite clear how it will work out in biology," says Shetty. "Do we need to make the debug cycle really quick, because our design tools aren't very good – or will our design tools mean that we don't need to be so quick to iterate our designs?"

You can't help but notice the engineering language in use here. Synthetic biologists use words and concepts that wouldn't be out of place building software or designing a bridge. But although the techniques are purposefully similar, the system design is not. Jim Haseloff explains: "If you're an electronic engineer it's all about components, where feedback is a special case and not the norm. A lot of synthetic biology is about making components, but as we move forward people are realising that if we want to build systems, we need to pay attention to intracellular communications and complex systems. What's exciting is that you can see these things coming together.

"Cells are many levels of order more complicated than any human artifact, and you just give them a bit of glucose."

Perhaps one of the most impressive synthetic biology projects is one from the Voigt Lab at the University of California in San Francisco. The first stage involved researchers there modifying *E.coli* to react to light. By growing a colony of these bacteria in a dish they created a biological "photographic film" – and one that, due to the small size of each bacterium, could theoretically work at resolutions of 100 megapixels per square inch. The second stage went further, producing *E.coli* that detects not only whether it is in the light or the dark, but whether it is at a border between the two. The new bacterium will turn black only if it's at one of these edges. You don't get a photograph, but rather a drawing of the outline of the image. Edge-detection is a well-known problem in regular computing. Your copy of Photoshop can detect edges, but as the picture gets bigger, the time it takes for the algorithm to work gets proportionally longer. With a biological system, there's no such time difference. Each cell makes its choice at the same time – the biological processor effectively runs in parallel.

"It's a beautiful story," says Vincent

Tom Knight, "father" of the field: "There's the famous headline: Synthetic Biology – Threat or Menace?"

'I want to create systems that are **still alive** but more simple, in order to build **useful new organisms'**
Tom Knight

PHOTOGRAPHY: JASON GROW

Rouilly of the project, "because they built on it year after year to make it more complex. You take what's already out there, you add some new parts, you modify some parts to make it better.

"One thing that I think is oversold in synthetic biology is that engineering gets things right the first time around. This is really far from the truth – engineering is all about tweaking."

Parallel processing is just one benefit of biological systems. But each feature of such systems brings an additional set of complications. As Reshma Shetty puts it, "What makes biology cool to work with is that it can self-replicate, but with that comes complexity we don't really understand."

To make things easier, Shetty and Rouilly sit on the committee of OpenWetWare.org, a Wiki that gives details of the techniques needed for such genetic engineering. It's a sort of recipe book for synthetic biology: "Grow a 5ml overnight culture of cells in LB media [a generic medium suitable for growing many species of bacteria]," reads the page on producing cells ready to take a BioBrick part. "In the morning, dilute this culture back into 25 to 50ml of fresh LB media in a 200ml conical flask. Aim to dilute the overnight culture by at least 1/100."

Much intellectual endeavour of the 21st century is based on such a philosophy of openness – where a field's knowledge and equipment are available to anyone, from the academic to the professional to the keen amateur hacker. Such open-sourcing brought us the internet and mashup culture. Just as the Arduino brings microelectronics to the hobbyist's kitchen table, as Linux opens up OS design to the amateur programmer, and as anyone with a Flip camera can make their own movie, BioBrick-based synthetic biology suggests a future where anyone with some lab kit from eBay could start engineering their own creatures. It's an idea that has inspired a growing community of amateurs to discuss "DIY bio" or "biohacking".

Some professionals don't see it quite that way. "On the whole, I think most members of this community are pretty naive," says Tom Knight. "In general, they think things are simpler than they are."

Amateur teams cannot enter the iGEM competition; the rules require standard lab equipment and professors to oversee projects. It's not because Knight and his team are against DIY bio per se, but rather that no group has yet shown itself to know what it's doing. Knight again: "In principle, it should be allowed. Well, sure – just show us you're minimally competent."

Vincent Rouilly agrees: "DIY bio is not part of the safety framework scientists work in, so that's a worry. In the lab, we forget how much built-in safety we have. For people to engage with synthetic biology, the field should develop a safe toolbox that would potentially limit crosstalk with the existing ecosystem. If you bought a computer, but when you plug it in there's a risk that you bring the whole network down, I don't think people would be so happy for everyone to have a computer."

For his part, Knight is sanguine about the risks "There's the famous headline: Synthetic Biology: Threat or Menace? If I wanted to be a bioterrorist, I wouldn't build a lab in my closet: I'd sift through cattlefeed to find anthrax spores."

He adds: "There are multiple levels at which this is absurd; potential terrorists are not that competent, and if they were, they'd understand there are better ways. There are thousands of people – millions around the world – in high-school labs doing experiments at the same level of risk, and nothing has crawled out of the petri dish yet. In fact, there haven't been any close calls at all."

Nevertheless, many are, in principle if not in specifics, worried about genetic engineering and synthetic biology – and safety concerns are treated very seriously by the UK government. The Health and Safety Executive insists on granting permission before a UK lab may be set up to perform any genetic engineering, even of simple bacteria – and it costs £490 just to apply.

But well-equipped universities do work in this field. Accredited students around the world are even now working on this year's iGEM entries. Tom Knight's past favourites include the University of Edinburgh's 2006 entry, addressing the problem of arsenic-contaminated water supplies in much of the developed world. In Bangladesh, 35 million people drink from contaminated wells. It doesn't take much arsenic to poison, but the usual tests require either sending the water to a lab – slow and expensive – or rely on field tests that require training, and which themselves create toxic byproducts.

So the team took biological parts from the iGEM kit, designed some of their own, and made a bacterium that changes the pH of the solution it lives in, according to the arsenic levels in the water added to it. This bacterium can be grown, dried, shipped to Bangladesh and then rehydrated with water from a suspect well. Dip in some old-fashioned litmus paper, and you learn how toxic that water is. It needs no training, and, as Knight puts it, the most expensive part of the test is the bottle that holds it: an elegant engineering solution, made possible by biology.

Quoting the aeronautical engineer Theodore von Kármán, Knight has the last word on the difference that mixing engineering with hard science has made: "Scientists discover the world that exists; engineers create the world that never was."

Ben Hammersley is associate editor of WIRED

AND LO, YOU CAN CREATE NEW LIFE

Self-flavouring yogurt

An Edinburgh University team genetically manipulated gram-positive bacteria. They could then add various sugars, each of which would create a specific flavour or colour, thus giving consumers plenty to choose from.

Nano-scale clothing

Freiburg University researchers designed a DNA strand that could be wrapped into specific shapes. Their products included "DNA dresses" for an imaginary nano-Barbie doll, and other nano-scale clothes.

Olive-oil quality detection

Students at Naples University created a glowing form of yeast as a way to detect the quality of extra-virgin olive oil. A red glow indicated that the oil was inedible; green meant that it was extra-virgin and ready to serve.

Multifunction probiotic material

A CalTech team launched a project to engineer microorganisms that could be housed in the human gut to combat problems associated with bacterial imbalances (such as lactose intolerance and conditions leading to birth defects). They worked with Nissle 1917, a commercially available probiotic strain of *E.coli*.

Glowing *E.coli*

A Sheffield University team wanted to develop a cheap and easy way to detect and prevent diseases caused by water contamination. The team manipulated *E.coli* cells so that they could detect the bacteria that cause cholera – by producing a green fluorescent glow in its presence.

Josie Allchin