UK Research and Innovation

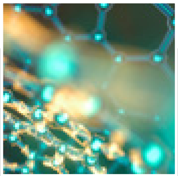
Engineering Biology

Solving real-world problems

Synthetic Biology is the design and fabrication of biological components, systems, and materials from biological elements for a useful purpose. Engineering biology is the process of taking those synthetic biology concepts and translating them into solutions to the problems people and the planet face, now and tomorrow.

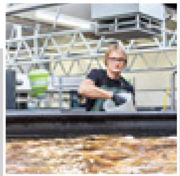
Engineering biology encompasses the entire innovation ecosystem, from breakthrough synthetic biology research to translation, commercialisation and application. It contributes to economic activity and sustainable and resource-efficient solutions to address societal challenges, and has applications across many sectors including energy, environment, food, healthcare and manufacturing. For example, Engineering Biology is already enabling the development of new vaccines and therapies, creating new materials for defence and fuels for transport, as well as plastic-free packaging and improved silk fibres for sports clothing.

This brochure outlines some of the engineering biology projects that UK Research and Innovation (UKRI) supports across a range of areas. It showcases how engineering biology research supported by UKRI is creating solutions to real-world problems both in the UK and around the world, and making a real difference to people's lives.







New blood

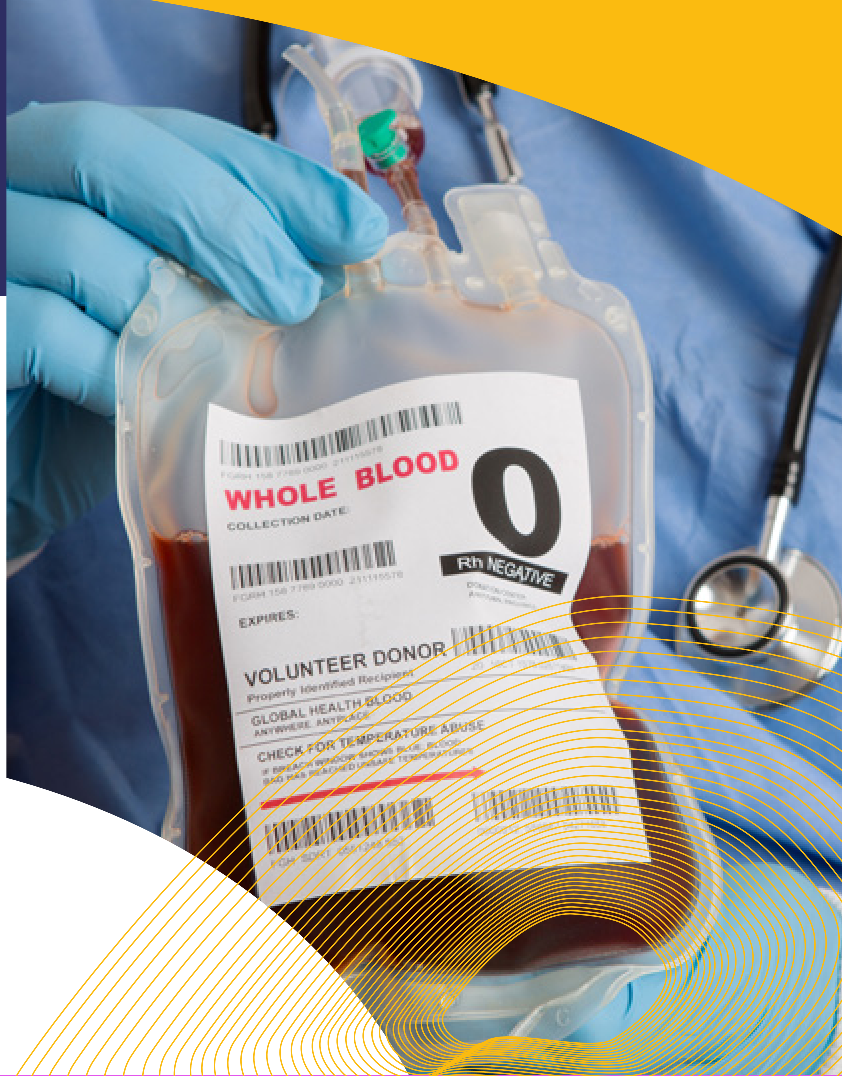
Developed with support from UKRI, new kinds of lab-made blood cells could have a wide range of therapeutic benefits.

Blood transfusions need to be carried out every day, but there is a shortage of supplies for people with rare blood types. As demand for safe blood increases worldwide, there is growing interest in the idea of artificially generating red blood cells.

The Synthetic Biology Research Centre BrisSynBio team, which is supported by BBSRC and EPSRC and based at the University of Bristol, has developed new techniques for making red blood cells in the lab: cells which could be used to help patients who cannot be matched with donor blood. Using gene-editing, the team has produced a more universal blood cell which has had five problematic blood groups removed.

At the same time the BrisSynBio team, in collaboration with NHS Blood and Transplant, have been opening up exciting new possibilities in relation to lab-made blood: engineering blood cells to have various kinds of therapeutic effect on patients, even in small volumes.

Ash Toye, who is Professor of Cell Biology at the University of Bristol, explains: “We had a general work stream around the idea of producing extra red blood cells for patients with rare blood types. The ambitious programme, which began in BrisSynBio in 2014, explored new ways of using lab-made blood therapeutically.

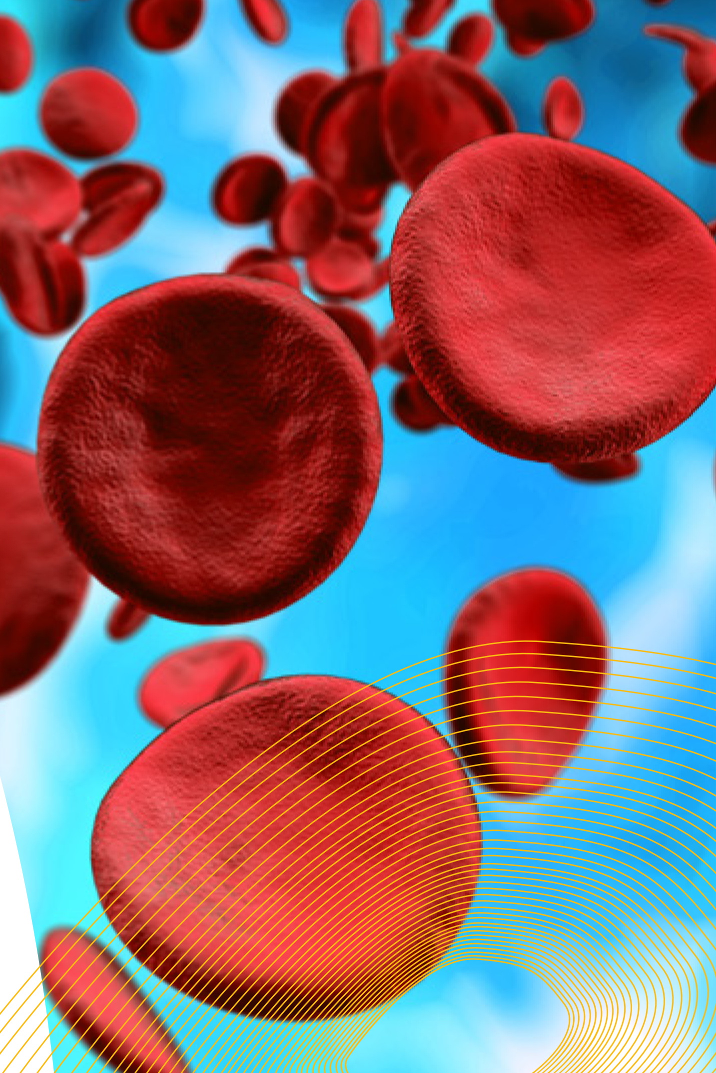


Making blood that can help people who have enzyme deficiencies, or using blood to carry medicines, or to stop people overdosing on drugs. For example, theoretically you could even have red blood cells that destroyed alcohol in the body, to protect the livers of people with alcoholism. We're interested in the idea of using blood cells like absorbent sponges, either soaking up or releasing chemicals that can pass through their membranes."

Ash Toye's team have a pending patent for the technique of creating freshly made red blood cells with enzymes inside them. "We started out to demonstrate proof of principle, by picking an enzyme that we thought would be straightforward, before we look to expand to other enzymes and produce more complex systems. We've recently published a key paper showing that you can keep certain enzymes within lab-grown blood cells throughout their development."

The team are exploring funding to continue developing these methods of putting enzymes in lab-made blood for therapeutic effect, with the aim ultimately of setting up a company to commercialise the work.

For Ash Toye, "the support that we received through BrisSynBio has allowed us to do things that might not have been possible with other kinds of funding: the key thing is that it gave us the flexibility to try different approaches. Sometimes you have an idea in your head, but you have no way of taking it forward: BBSRC helped to get us to the point of being able to demonstrate proof of principle. The reward for this support is that we now have something which is flexible to use, and which has potential to be commercialised."



SimCells

New kinds of reprogrammable cell have huge potential for healthcare, sustainability – and helping us understand life itself.

SimCells – short for simple cells – are "like computers that have been reinstalled with a new operating system," according to Wei Huang, Associate Professor of Engineering Science at the University of Oxford. "The hardware – the structure and machinery of the cell – stays the same, but the native chromosome is taken out, and replaced with an artificial and designed gene-circuit for operating instructions. SimCells are like 'bio-robots,' little cellular machines."

What this means for synthetic biology, which is about engineering organisms to make them perform specific functions, is potentially revolutionary. What Professor Huang's team have shown, in the EPSRC-funded project 'development of SimCells as building blocks for synthetic biology,' is that SimCells can be created relatively easily from living bacteria, that they can be used safely and reliably, and that they have huge potential, being able to be 'programmed' for a wide range of tasks.

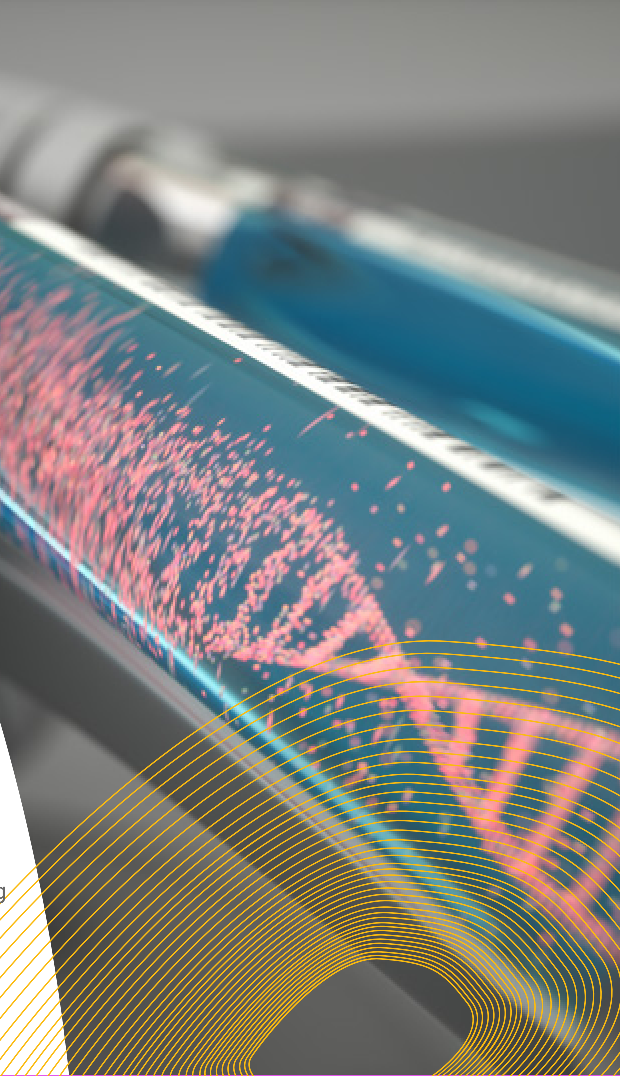
"People sometimes worry about genetically modified organisms (GMOs), but if we're to use synthetic biology to solve real-world problems, we have to take these concerns seriously," says Professor Huang. "With modified natural cells, you're always fighting against nature – the native chromosome, which has evolved over millions of years, is always trying to assert itself, trying to survive and to replicate, and the natural 'programming' of the cell is always interfering with the new task that synthetic biologists want to give it. Then, where synthetic biology wants reliable, predictable cells to work with, cells modified from nature will always have the biological variability that is common to all organisms that evolve."

SimCells by contrast are highly controllable. They're designed solely for a specific purpose, and put most of their energy into doing just that – they won't replicate, or fight against the function that they're given. There's no danger of a SimCell escaping and proliferating in nature, and so they're more acceptable to public opinion than GMOs. But SimCells keep enough of their original biomolecular machinery still to be able to synthesise proteins, which gives them huge potential.

Some teams are now looking at using SimCells to synthesise bio-fuels (alkanes and ethanol in particular), but the spin-out that Professor Huang is involved with, Oxford SimCell, is focusing on applications in healthcare.

SimCells have been shown to work well in diagnostics – they can be designed to bind to particular viruses, and so could be used to detect them, quicker and cheaper than the purified enzymes that are usually employed for this purpose. Then, SimCells could potentially be used to treat cancer. It's been shown that they can convert common aspirin into catechol, a potent anti-cancer drug. SimCells could be designed specifically to anchor on the surface of some cancer cells, and then be induced to release catechol in a highly concentrated and targeted way, attacking the cancer cell repeatedly over time, until it is out for the count. There is even the potential to use SimCells to create a vaccine, which would prevent people from getting certain cancers in the first place.

While these applications are being developed, Professor Huang's team continue to work on some fundamental research questions, such as how to keep SimCells functioning longer – how to refresh them or repair them, to get energy to them, and prevent them from wearing out. And if finding new treatments for cancer and helping to solve the climate crisis weren't enough, research on SimCells could also shed light on some fundamental questions about the nature of life at the most basic level. Not bad for a relatively new research area.



Off the wall

The huge success of a Synthetic Biology spin-out demonstrates some important truths about the public funding of research.

In 2018 the media was awash with stories about university spin-out Ziylo, after it was acquired by Danish company Novo Nordisk, one of the world's leading manufacturers of diabetes medicines. The deal was potentially worth up to $800 million, making it one of the most valuable acquisitions of a UK spin-out in recent years.

Ziylo was founded in 2014 to commercialise research in the University of Bristol chemistry lab of Professor Anthony Davis. Professor Davis's team had found a way to design synthetic molecules that bind to glucose in blood: by attaching these glucose-grabbing molecules, it should be possible to create a radically new form of insulin that is active when glucose levels are high, but not when they fall. Currently, having too much active insulin in their bodies means that diabetic patients run the risk of having 'hypos' – episodes of hypoglycaemia, when blood sugar levels fall dangerously low, potentially leading to seizures, coma and even death.

'Smart' insulin could help change the lives of millions of people for the better. Diabetes is a growing problem, with rising levels of obesity around the world: more than 400 million people are thought to be living with diabetes (around four million of them in the UK), and some 1.6million deaths a year are attributable to the condition.

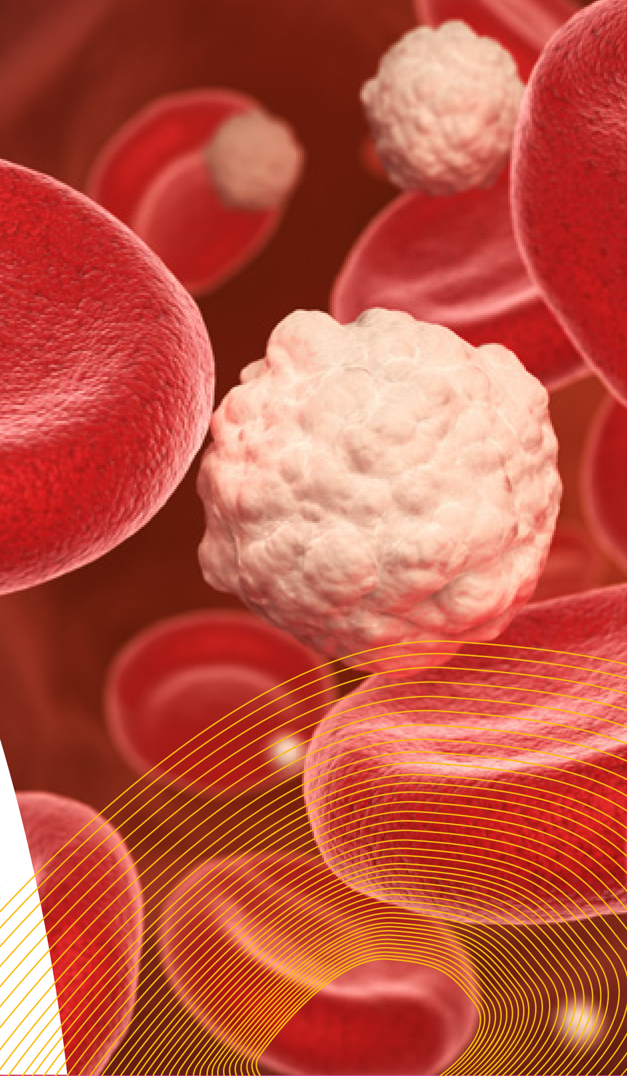
On the face of it, this might seem a simple story of UK research expertise generating discoveries with huge commercial potential. But according to Professor Davis, the route to Ziylo's breakthrough was anything but straightforward, and it illustrates some important aspects of the public funding of research.

"This was a problem that I first started thinking about 30 years ago: how you make molecules that bind with certain other molecules, but with nothing else. For most of that time I never thought that this would be of more than academic interest. We were pottering along with the work for maybe 25 years, when suddenly we came across one molecule that binds only with glucose, and that can do so not just in the lab, but under the more messy conditions inside the body. All at once we had something that was good enough to take to market."

The breakthrough came about largely through the critical work done by Robert Tromans, who was then a PhD student at Bristol's EPSRC Centre for Doctoral Training in Chemical Synthesis, where Professor Davis is a supervisor.

At other important points, too, public funding supported the team's work, including through two EPSRC postdoctoral grants and two EPSRC Impact Acceleration Awards. Ziylo also received funding through ICURe, an Innovate UK programme which helps university researchers explore the commercial potential of their work.

"The support we had from EPSRC and Innovate kept us going along the way," says Professor Davis. "Public funding supported us, when for much of the time our research looked so off the wall that it would have been difficult to interest private investors." For Professor Davis, the route to Ziylo's acquisition ultimately shows that it can be very hard to predict what academic research will end up paying off: "it's a strong argument for trying out different ideas, and seeing what they lead to."



Sweet taste of success

Innovative biotechnology has led to less expensive and more sustainable flavourings.

A new method of producing grapefruit flavouring from orange oil has been developed by researchers at the University of Oxford, thanks to funding from EPSRC and BBSRC. The grapefruit flavouring is the first innovative product to be marketed by spin-out company Oxford Biotrans, and marks the culmination of nearly two decades of research in biotechnology.

Grapefruit flavouring is in high demand but short supply. Around 20 tonnes of nootkatone, which is what gives grapefruit its flavour and fragrance, is used around the world every year, yet it takes 400,000kg of grapefruit to produce just 1kg of nootkatone. As a result, nootkatone extracted from grapefruit is expensive: worth up to $7,000 per kg (or $35 for just one teaspoon). Alternatively, nootkatone can be produced synthetically, but this takes a great deal of energy, and uses harsh reagents that generate toxic by-products.

Professor Luet Lok Wong and his colleagues in the Department of Chemistry at the University of Oxford have found a way to create nootkatone from orange flavouring, which is plentiful, using a particular form of an enzyme called cytochrome P450. This process is more environmentally sustainable than synthetic production and, because the nootkatone is created through a biological process, it can be labelled as 'natural' under EU regulations, which makes it more palatable to consumers.

“We’ve shown that variants of this enzyme can catalyse a lot of different reactions,” explains Matthew Hodges, Director of Commercial Operations at Oxford Biotrans, “so we can create a lot of different products using it. We’re using nootkatone as an example in the first instance, to prove that we can produce it economically and on an industrial scale. But in the longer term we plan to show that we can make not just flavours and fragrances, but other fine chemicals too – including pharmaceuticals and nutraceuticals. We aim to show that industrial biotechnology can be used to replace traditional chemistry in many different industries.”

The creation and patenting of the P450 enzyme, and the launch of commercial products that are based on it, has been the result of around 20 years of research by Professor Wong and his team, with support from EPSRC and BBSRC.

“The great thing about the funding from EPSRC and BBSRC,” says Matthew Hodges, “was that it helped enable the proof-of-concept and even pre-proof-of-concept work to be performed, at a stage when it would have been impossible to make a case for private investment, because the science was still unknown.”

The company, which has now received over £7 million in private backing, is continuing to develop and commercialise products based on enzyme technologies that yield high-value chemical compounds. Using natural, readily-available feedstocks not only helps the environment and reduces costs, it also offers security of supply at a large scale – a sweet solution all round.

Synpromics

New techniques in gene therapy, developed with the support of Innovate UK, could lead to more targeted treatments.

For people with a range of serious and previously untreatable genetic disorders, such as Huntington's disease, Duchenne Muscular Dystrophy and cystic fibrosis, gene therapy offers the possibility of effective treatment, or even cure. Gene therapy involves modifying a person's genes: it can mean replacing a disease-causing gene with a healthy copy, or activating or inactivating a gene that is not functioning properly.

Gene therapy has long been hampered by the difficulty of controlling and precisely targeting these processes, so that the genes that are required are expressed only within particular organs, or even particular cells, and nowhere else. But with long-standing support from Innovate UK, an Edinburgh-based company has developed new techniques, that allow gene therapies to be much more precise and controllable.

Synpromics's founder and CSO Dr Michael Roberts explains: "For gene therapy to be effective, genes need to be able to be switched on and off in a controlled way. In the past, the gene therapy community has used parts from viruses to switch genes on and off, but at Synpromics we developed a technique that uses parts of the human genome to create synthetic switches, which can be controlled more precisely. They enable therapies to be much more selective in the way they work."

Synpromics was developing this technique just at the time that Innovate UK was focusing on synthetic biology as an important and emerging research area. "The technique had a range of possible applications within the broad field of biotechnology," says Michael Roberts, "and Innovate supported a series of research projects to show how the technology could work in different areas."

The projects examined the potential of the new technique for developing vaccines, for improving the manufacturing of biological drugs in mammalian cells, and for developing new pathways in yeast for use in industrial biotechnology. Eventually it became clear that gene therapy was the area with the greatest potential, and where the new technique could have the greatest benefit. Synpromics then worked on a project to improve gene therapy manufacturing processes with the Cell Therapy Catapult, one of the UK's network of Catapult centres, which is focused on developing and growing a cell and gene therapy industry in the UK.

With the acquisition of Synpromics by American company AskBio in 2019, the technique now has the potential to be translated into specific gene therapies on a large scale. AskBio are specialists in developing viral vectors that carry therapeutic genes into cells: by pooling their gene therapy technologies with those of Synpromics, it should be possible to make gene therapies that are more targeted and controllable than current ones.

After the acquisition of AskBio by Bayer in 2020, Synpromics continues to play a key role in early stage product development, still with its headquarters in the UK. The company has gone from having four or five people in the lab, when it first began to be supported by Innovate UK, to employing around 50.

By joining with AskBio there is the potential not just to develop new gene therapies, but to manufacture them in-house. Several are now in the pipeline, with results expected in the next few years; tackling such disorders as the often-fatal inherited Pompe disease, and the fatal gene disorder Huntington's disease.

For Michael Roberts, "our vision ultimately is to develop treatments for diseases beyond the monogenetic disorders, which are what gene therapy has tended to focus on (disorders such as sickle cell anaemia, cystic fibrosis and Duchenne Muscular Dystrophy, which are the result of a single defective gene). With greater gene control, there is potential for us also to develop therapies for larger pathway diseases that are more complex."

Fermenting a revolution

With UKRI support, a British company is making clean fuels from waste products.

It’s been known for some time that microbes can be used to break down various waste materials, producing a clean form of fuel as they do so. The trouble has been that to do this at scale has taken significant capital outlay: the production plants it requires don’t come cheap. But now a British company is using novel microbes and scaled-back technology, to make fuel from waste a much more feasible proposition.

C3 Biotechnologies is a spin-out from SYNBIOCHEM, the University of Manchester’s Synthetic Biology Research Centre for Synthetic Biology of Fine and Speciality Chemicals, which since 2014 has been supported by BBSRC.

C3’s Science Director, Professor Nigel Scrutton, explains: “The origins of our work are in an EU Framework Programme grant from 2010, which first enabled us to get involved in engineering microbial strains to make fuels. Then as BBSRC began to invest in SYNBIOCHEM in 2014 we were able to accelerate this work, and within a year we had registered the company, to commercialise some of the tools and technologies we were developing.”

In the last seven years C3 has really taken off: where initially the company was focused on making propane from waste materials, it now offers several different products in the fuel-from-biology sphere, including bio-ethanol and precursors to aviation fuel.

What these products have in common is that they are all clean forms of energy, made from industrial, agricultural and food waste. All are carbon-neutral: in some cases CO_2 is even used as a feed stock, reducing the amount of greenhouse gases in the atmosphere. And when water is needed to make them, seawater can be used instead of fresh water.

As Nigel Scrutton says, “a significant hurdle in this area has long been the capital investment needed to build fuel production plants. We took a step back, working-up technologies that pulled away from needing sterile conditions and big steel bio-reactors, and headed towards something much simpler. You could grow our bacteria in a plastic bag.”

“We’ve looked at all aspects of the process, to get costs down. We also use microbes that generally haven’t been used before in industrial plants.” C3 has a number of patents granted around these innovations, and is now working as a commercial partner on major projects, including the development of bio-based production routes for aviation fuel precursors at scale.

In itself, biomanufacturing fuels from waste may not be enough to solve the climate crisis. But it offers a way of continuing to use carbon-based fuels without increasing the amount of CO_2 in the atmosphere: these fuels can simply be dropped into our existing infrastructure and distribution systems, and used in the transport that we currently have.

The UK is a world-leader in lab-based academic research into the production of fuels from waste, using fermentation and photo-catalytic processes. With BBSRC support through SYNBIOCHEM, it seems that British companies are finally in a position to begin capitalising on this research excellence.

Colour me good

Synthetic biology is leading to new kinds of sustainable dyes.

The dyeing of textiles is big business: the global market is worth around $9.8 billion a year. But it's also a business that has a serious effect on the environment. The dyes themselves are mostly synthetic – deriving from petrochemical sources – and highly toxic, with a nasty habit of ending up as effluent – textile dyeing accounts for over 20% of global industrial water pollution. Huge amounts of energy and water are used in the dyeing process: conventional dyeing has to be done at high temperatures, and the industry is one of the world's thirstiest, consuming over 5.8 trillion litres of water a year.

With consumer pressure growing, and increasing demand for stronger regulation of the textile dyeing industry, a British company is developing innovative solutions to the problem of harmful dyes, building on recent advances in synthetic biology. With support from Innovate UK, Norwich-based Colorifix has developed the first entirely biological process to produce, deposit and fix dyes onto textiles.

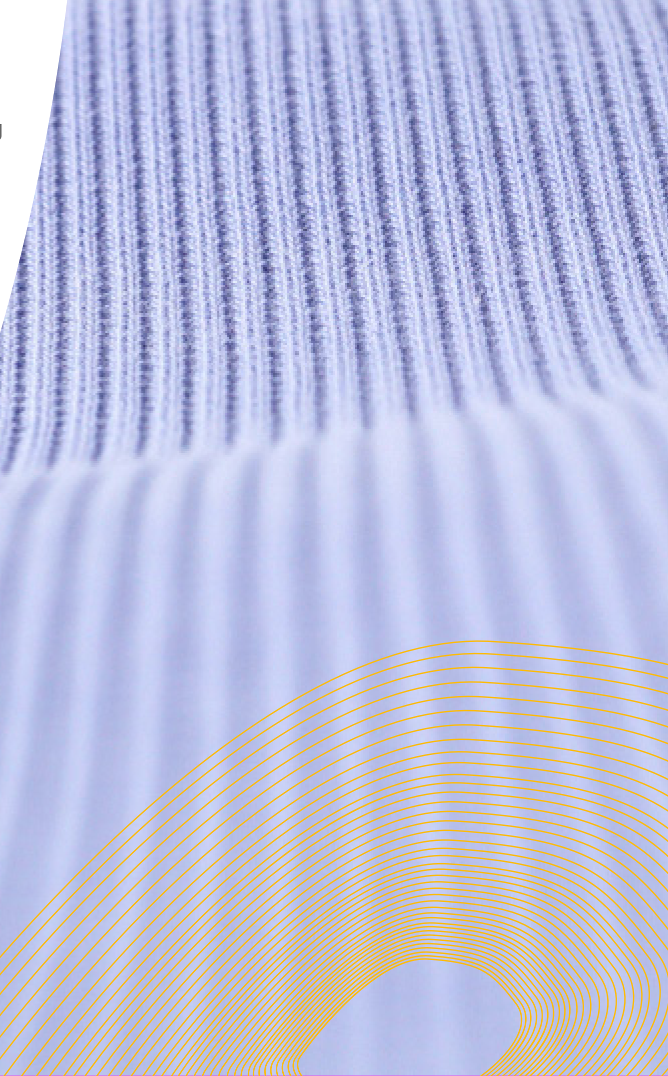
Neil Williamson, who is Head of Microbial Engineering at Colorifix, explains: "Our work is about engineering natural solutions to man-made problems. Our aim is to change the textile dyeing industry to something more environmentally friendly, socially responsible, and economically viable."

“The first step in our process is to identify a pigment that is produced by an organism in nature— whether a plant, animal, insect or microbe. Rather than working with a physical specimen, we use DNA sequencing and bioinformatic tools to identify the exact genes and enzymes that are responsible for the production of the targeted colour. We then build and translate that information into our non-pathogenic microbe that can produce, transfer and fix colorants in one unique and integrated process.”

The textile industry needs dyes that are uniform, colour-fast and economical to produce, and using engineered bacteria helps to meet these criteria consistently, with considerably reduced environmental impact. As well as meeting industry standards for colour-fastness, the new dyes have also been validated as non-allergenic.

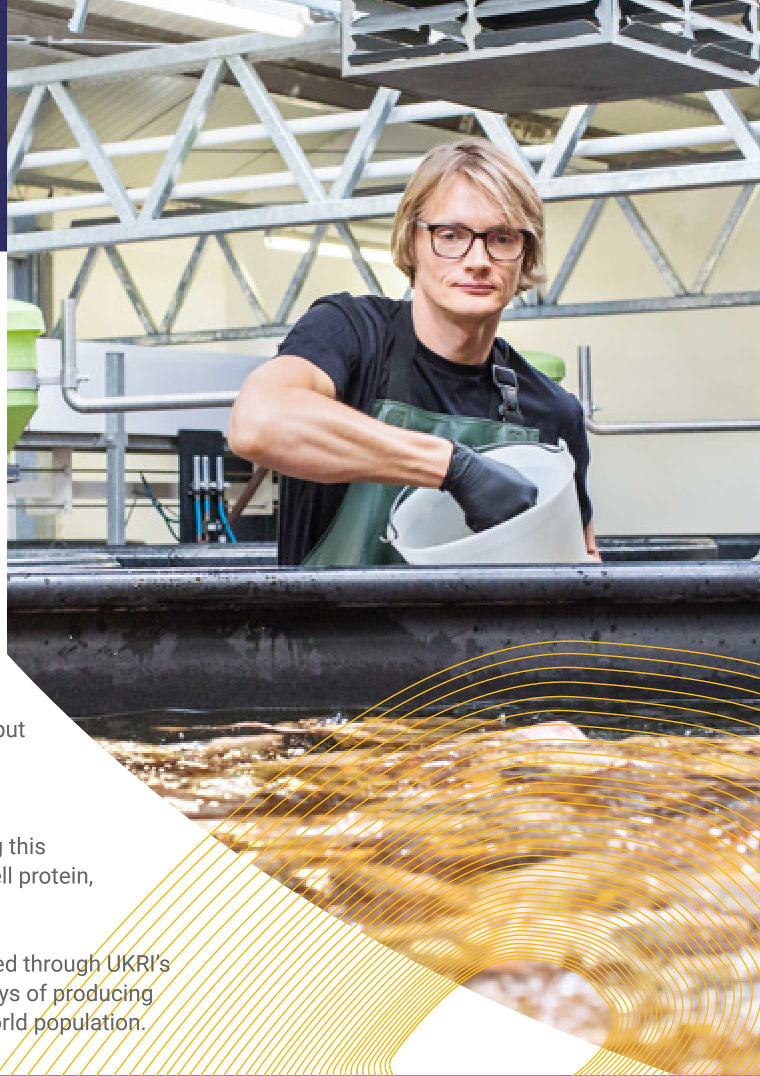
Some of the new pigments even have significant potential in the fight against dangerous viruses and bacteria. A second Innovate-funded project aims to produce antiviral dyes that can combat the coronavirus responsible for the COVID-19 pandemic. With researchers at the University of Cambridge, the project involves developing pigments that, when applied to textiles in a hospital setting or, for example, to the fabric of seats on trains, deactivate coronaviruses and other viruses and bacteria that are responsible for serious respiratory conditions.

With clients including clothing giants H&M, Colorifix has grown from having four employees when it was founded in 2016, to 36 now. As one of several innovative companies based in Norwich Research Park, Colorifix is also contributing to the development of a synthetic biology hub in East Anglia. For Neil Williamson, “Innovate funding has enabled us to work with some outstanding academic partners, to develop challenging, innovative processes that make a real difference to people’s lives.”



Deep Branch

Microbes that turn CO_2 into protein could help feed a growing population.



As the global population grows, we're faced with a dilemma. We need to produce more food (it is estimated that 60% more will be needed by 2050), with increasing demand for protein in particular. But at the same time we need to make food more sustainable: currently, food production is a major source of carbon emissions.

What if we could produce food in a way that doesn't just minimise carbon emissions, but takes waste products from other industries, and makes use of them? A UK/Dutch start-up has developed a method for doing just that: taking carbon dioxide from industrial plants and transforming it into a safe, nutritious and sustainable protein for use in feed for fish and poultry.

Nottingham-based Deep Branch uses microorganisms to convert clean CO_2 into high-quality products. Rather than using sugar, the main feedstock that is normally used, its microbes are fed carbon dioxide. They then produce a protein that offers a comparable nutrient profile to fishmeal, but comes with a 90% smaller carbon footprint.

Building on previous Innovate UK funding to help develop the proprietary gas fermentation technology, the REACT-FIRST project is now testing and trialling this radically more sustainable way of making feed, and the new type of single-cell protein, called Proton™, is the result.

REACT-FIRST is one of a number of research projects that are being supported through UKRI's £90 million Transforming Food Production Challenge, looking to find new ways of producing food that reduce emissions and pollution, while helping to feed a growing world population.

REACT-FIRST, which has received £3 million in funding through Innovate UK, brings together a consortium of 10 industry and academic partners, covering the whole CO2-to-food pipeline: they include energy generator Drax, BioMar and AB Agri (producers of feed for fish and animals respectively), and supermarket Sainsbury's, representing the end-consumer.

At the same time, researchers from the Sustainable Aquaculture Innovation Centre, the Innogen Institute and the Universities of Nottingham, Stirling and Nottingham Trent will be gathering critical data about how Proton™ works as a fish and poultry feed: its cost, digestibility, nutritional quality and carbon footprint. They will also be looking to develop strains of bacteria that will work more efficiently in the process – growing quicker and producing protein more consistently.

REACT-FIRST began in July 2020: a successful outcome will enable the new process to be scaled-up and commercialised. And the consequences of that could be significant – as Deep Branch's Communications and Grant Manager Polly Douglas explains, "if you look at what Proton™ could displace as fish and animal feed, it includes soya (whose cultivation often leads to rainforests being cut down) and fish meal which is shipped from South America (with the carbon footprint that this leads to)."

Currently, most of the UK's animal feed protein comes from overseas, so there's an important food security issue here, as well as an environmental one: making protein in the new way would make the UK less dependent on complex and sometimes fragile supply chains. What's more, the new process makes it possible to grow food on brown-field sites (it doesn't need arable land, and so doesn't compete with production of food for humans), and it takes much less space than traditional agriculture.

Deep Branch is so named because bacteria that are used in the CO2-to-food process come from some of the oldest branches on the evolutionary tree. And like its microbes, the company is growing – in the last year it has doubled in size, with 20 people now working in highly skilled jobs.