the limitations of our current technology," says Edward Chang, a neuroscientist at the University of California, San Francisco (UCSF), who is leading one of the projects.

DARPA is supporting Chang's group and another at Massachusetts General Hospital (MGH) in Boston, with the eventual goal of treating soldiers and veterans who have depression and post-traumatic stress disorder. Each team hopes to create a system of implanted electrodes to track activity across the brain as the organ is stimulated. The groups are developing their technologies in experiments with people with epilepsy who already have electrodes implanted in their brains to track their seizures.

At the SfN meeting, electrical engineer Omid Sani of the University of Southern California in Los Angeles — who is working with Chang's team — presented the first map of how mood is encoded in the brain over time. He and his colleagues worked with six people with implanted electrodes for epilepsy, tracking their brain activity and moods over one to three weeks. By comparing the two types of information, the researchers could create an algorithm to 'decode' that person's changing moods. Some broad patterns emerged, particularly in brain areas associated with mood.

Chang and his team are ready to test their new single-closed-loop system in a person, Sani says. Chang adds that the group has already tested some closed-loop stimulation in people, but he declined to provide details because the work is preliminary.

The MGH team is taking a different approach. Rather than detecting a particular mood or mental illness, the researchers want to map the brain activity associated with behaviours that are present in multiple disorders — such as difficulties with concentration and empathy. At the SfN meeting, they reported on tests of algorithms that stimulate the brain when a person is distracted from a set task, such as matching images of numbers or identifying emotions on faces.

"You have to do a lot of tuning to get it right."

The researchers found that delivering electrical pulses to areas of the brain involved in decision-making and emotion significantly improved participants' performance. The team also mapped the brain activity that occurred when a person began failing or slowing at a set task because they were forgetful or distracted, and reversed it with stimulation. They are now beginning to test algorithms that use specific patterns of brain activity as a trigger to automatically stimulate the brain.

Wayne Goodman, a psychiatrist at Baylor College of Medicine in Houston, Texas, hopes that closed-loop stimulation will prove a viable long-term treatment for mood disorders — partly because the latest generation of algorithms is more personalized and based on physiological signals, rather than a physician's judgement. "You have to do a lot of tuning to get it right," says Goodman, who is about to launch a small trial of closed-loop stimulation to treat obsessive–compulsive disorder.

One challenge when stimulating areas of the brain associated with mood, he says, is the possibility of creating extreme happiness that overwhelms all other feelings. Other ethical considerations arise because the algorithms used in closed-loop stimulation can tell the researchers about the person's mood, beyond what may be visible from behaviour or facial expressions. "We will have access to activity that encodes their feelings," says Alik Widge, a psychiatrist and engineering director of the MGH team. Like Chang and Goodman's teams, Widge's group is working with neuroethicists to address the ethical concerns surrounding its work.

Still, Chang says, the technologies that his team and others are developing are only a first step towards better treatment for mood disorders. He predicts that data from trials of brain implants could help researchers to develop therapies that stimulate the brain through the skull. "For the first time," he says, "we're going to have a window on the brain where we know what's happening in the brain when someone relapses." ■

BIOLOGY

Cells use 'alien' DNA to make protein

Expanded genetic alphabet could allow for the production of new protein-based drugs.

BY EWEN CALLAWAY

Life has spent the past few billion years working with a narrow alphabet. Now, researchers have broken those rules by adding extra letters to biology's limited lexicon.

Chemist Floyd Romesberg of the Scripps Research Institute in La Jolla, California, and colleagues manipulated *Escherichia coli* bacterial cells to incorporate two types of foreign chemical bases, or letters, into their DNA. The cells used that information to insert unnatural amino acids into a fluorescent protein.

Organisms naturally encode heritable information using just four bases: adenine (A), thymine (T), cytosine (C) and guanine (G). These form pairs that hold together DNA's double helix, and different three-letter sequences code for each of the 20 amino acids that make up proteins in living cells. The latest work, reported in *Nature* on 29 November, is the first to show that unnatural bases can be used to make proteins in a living cell (Y. Zhang *et al. Nature* http://dx.doi.org/10.1038/nature24659; 2017).

The result, Romesberg says, shows that synthetic biology — a field focused on imbuing organisms with new traits — can accomplish its goals by reinventing the most basic facets of life. "There is no biological system so fundamental and more intimately related to what we are than information storage and retrieval," he says. "What we've done is design a new part that functions right alongside the existing parts and can do everything they do."

Several teams are attempting to expand the genetic code. The 4 natural DNA bases can be arranged in 64 different 3-letter combinations, called codons, that specify amino acids. But redundancy in this code — for instance, CGC, CGA, CGG and CGT all stand for the amino acid arginine — means that nearly all proteins needed for life are made of just 20 amino acids.

Some researchers, including geneticist George Church of Harvard Medical School in Boston, Massachusetts, are repurposing redundant codons to specify new amino acids. Romesberg's group is exploring a different strategy: adding an entirely new base pair into DNA. That would vastly increase the number of possible codons, in theory giving cells the ability to exploit more than 100 extra amino acids.

Although Church still thinks that his own approach is more practical for most applications, he describes the new work as a "milestone in exploring the fundamental building blocks of life".

NATURAL FIT

To function in living cells, foreign base pairs need to sit alongside natural bases without disturbing the shape of DNA or disrupting essential tasks, such as the processes that faithfully copy DNA and transcribe it into messenger RNA — an intermediary molecule between DNA and proteins. In 2014, Romesberg's lab

reported an *E. coli* strain with a loop of DNA containing a single unnatural base pair (D. A. Malyshev *et al. Nature* **509,** 385–388; 2014). But the cells divided sluggishly, and tended to lose their foreign DNA over time. In the latest research, the team created healthy cells with extra bases made of chemicals called dNaM and dTPT3 (dubbed X and Y, respectively).

And they can finally wield their foreign DNA. In separate experiments, the cells incorporated two unnatural amino acids (called PrK and pAzF) into a protein that emits a soft, green glow (see 'A foreign language'). Both the foreign bases and the amino acids were fed to the cells, and any organism that somehow escaped the lab would not be able to produce them. To allow the cells to use these components, the researchers created modified versions of molecules called tRNAs, which read codons and ferry the appropriate amino acids to the cells' protein factories — ribosomes.

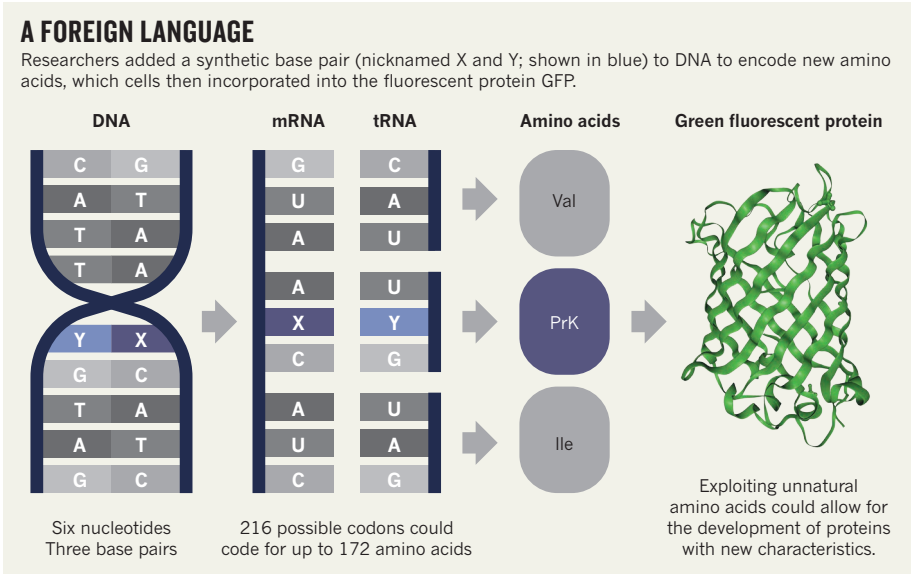
The new amino acids did not change the shape or function of the green fluorescent protein. But "now that we can store and retrieve information", says Romesberg, "let's do something with it". In unpublished work, his team has inserted a foreign base pair into a key site in the gene implicated in antibiotic resistance. Bacteria that shed their foreign DNA become sensitive to penicillin-related drugs.

Romesberg has started a biotechnology company, Synthorx in La Jolla, which is attempting to incorporate unnatural amino acids into protein-based drugs such as IL-2, which regulates numbers of white blood cells. The approach could lead to drugs that, for example, are taken up by cells more easily, or that are less toxic or break down more quickly. Proteins could also be designed to have properties that conventional amino acids lack, such as the ability to strongly attract electrons. "It's like being a kid in a candy store," says Romesberg. But in this case, "the kid spent 20 years fantasizing about getting into that candy store. All of sudden I'm thinking what kind of candy can I get."

Teams led by chemist Steven Benner of the Foundation for Applied Molecular Evolution near Gainesville, Florida, and Ichiro Hirao, a biological chemist at the Institute of Bioengineering and Nanotechnology in Singapore, have already developed test-tube systems for using foreign DNA to encode unnatural amino acids. Hirao sees advantages to moving into living cells. Proteins containing unnatural amino acids could be made more quickly and cheaply using bacterial cells, he says. Bringing the technology to eukaryotic cells would allow development of new antibody-based drugs, too.

But Benner suggests that because Romesberg's system relies on relatively weak hydrophobic forces to hold foreign base pairs together, its potential for industrial applications might be limited. Cells may tolerate the rare foreign base, Benner says, but "one simply cannot build an entire genetic system from them".

Romesberg and his colleagues are now working on expanding their genetic alphabet further. So far, the team has identified 12 more codons containing X and Y that are functional, says Romesberg, but "there's a lot yet to do". ■



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POLICY

Britain pins economic hopes on science

Industrial strategy splashes cash on research.

BY ELIZABETH GIBNEY

The United Kingdom has laid out how it will pour money into research to boost its economy — including cash for artificial intelligence and other high-tech industries — as the country prepares to leave the European Union in 2019.

Science does not usually sit at the forefront of British economic-policy documents. But the UK government's new industrial strategy, released on 27 November, is sprinkled throughout with references to research and development (R&D), highlighting a focus on research as a remedy for economic woes. "It feels like science permeates this strategy," says Graeme Reid, a science-policy researcher at University College London.

The shift in emphasis will change expectations, says Paul Nightingale, deputy director of the Science Policy Research Unit at the University of Sussex in Brighton, UK. Historically, commercializing research has not been seen as a strength of the UK universities system. But in return for R&D cash, universities will now be expected to increase their commercial focus and interaction with local businesses, he says: "This isn't 'strings attached', this is ropes. My impression from talking to lots of academics is that they don't understand how big this is."

The industrial strategy is an effort to boost UK productivity — economic output per hour worked — which has stagnated since the financial crisis and lags behind that of other industrialized nations. In part to counter that trend, the government has promised to massively boost R&D spending: from 1.7% of gross domestic product (GDP) in 2015 to 2.4% by 2027. (By comparison, Germany already spends 2.9% of GDP on research; the United States, 2.8%).

UK scientists have already been promised boosts in public spending. Last year, politicians committed to yearly increases in research funding until 2020–21; last week, they announced that they would continue that increase in 2021–22, raising public research funds by a further £500 million (US$667 million), to £12.5 billion. To raise private spending, the government promises to work with industry to produce a road map in the coming months; UK chancellor Philip Hammond ▶