

themselves. The idea behind the new targeted approaches is to eradicate specific stem cells to make room for transplanted cells without the side effects of existing treatments, which destroy bone marrow cells indiscriminately.

Physicians currently rely on full-body radiation or treatment with toxic, DNA-damaging chemotherapy drugs to kill existing blood stem cells and clear the way for the transplanted cells to repopulate the marrow. That preparation kills not only blood stem cells, but also a host of other cells in the marrow. This can cause infertility, seed cancers that occur later in life, and severely compromise the immune system, leading to lengthy hospital stays.

“It’s really prohibitive for patients,” says David Scadden, a stem-cell biologist at Harvard University in Cambridge, Massachusetts. “This technology just won’t be adopted unless we really change the whole dynamic.”

Stem-cell hotel

One way to think about stem-cell transplants is that the bone marrow is a hotel whose owner wants to evict some guests, says Jens-Peter Volkmer, vice-president of research at Forty Seven, a biotechnology company in Menlo Park, California. Current treatments blow up the whole hotel, he says. “Then everybody’s dead, including all of these critical components that you need to protect the patient from infection.” The latest approaches allow the owner to tell specific guests to leave – by targeting sets of cells in the bone marrow, rather than killing them all, Volkmer says.

At the haematology meeting, which begins on 7 December, researchers from Forty Seven will present the results of studies that tested a combination of two antibodies in monkeys. One antibody blocks the activity of a molecule called c-Kit, which is found on blood stem cells and is vital to their function; the other inhibits a protein called CD47, which is found on some immune cells. Inhibiting CD47 allows those immune cells to sweep up the stem cells targeted by the c-Kit antibody, making way for new cells.

In the tests, the combination reduced the number of blood stem cells in bone marrow. But the team has not yet demonstrated that the treatment clears out enough old cells to allow transplanted cells to flourish.

Another company, Magenta Therapeutics of Cambridge, Massachusetts, has collaborated with researchers at the US National Institutes of Health to test a different antibody, which binds to c-Kit and then releases a toxin to kill the blood stem cell that produced the protein. Data from studies in mice and one monkey suggest that this can kill off enough stem cells in the bone marrow for transplanted cells to thrive – without destroying other cells such as immune cells.

And a team led by transplant physician Judith Shizuru at Stanford University in California

has tested a similar approach in babies with a genetic disorder that cripples the immune system. The researchers, in a collaboration that includes the firm Amgen of Thousand Oaks, California, used a third antibody that targets c-Kit. The team found that transplanted stem cells, in this case from donors who did not have the disease, successfully took hold in the bone marrow of four out of six of the babies.

Expanding market

These developments come as the potential market for blood-stem-cell transplants is expanding, says Mani Foroohar, an analyst at SVB Leerink investment bank in Boston, Massachusetts.

Some gene therapies, such as one recently approved by European regulators to treat a genetic immune disorder called ADA-SCID, use a version of the technique. They remove the patient’s blood stem cells, then genetically modify them so that they are free of the disorder before infusing them back into the body. Magenta and Forty Seven have entered

into separate collaborations with researchers developing gene therapies to treat blood disorders such as β -thalassaemia and sickle-cell disease (see page 22).

And data are accumulating to show that some people with type 1 diabetes, systemic sclerosis and other autoimmune disorders can enter long-lasting remission if the mature immune cells in their bone marrow are wiped out and replaced with an infusion of their own blood stem cells (E. Snarski *et al. Bone Marrow Transpl.* **51**, 398–402; 2016; K. M. Sullivan *et al. N. Engl. J. Med.* **378**, 35–47; 2018). The procedure is thought to reset the immune system by eradicating cells that are attacking the body’s own tissue, says Keith Sullivan, a stem-cell transplant physician at Duke University in Durham, North Carolina.

Sullivan says that the early data from Shizuru and others are intriguing, and that he has begun discussions to collaborate with researchers in the field. “The train is moving now,” he says. “The question is, how do we do this in the right way?”

CARBON DIOXIDE-EATING BACTERIA OFFER HOPE FOR GREEN PRODUCTION

Lab workhorse *E. coli* engineered to make nutrients from greenhouse gas rather than from sugars.

By Ewen Callaway

E*scherichia coli* is on a diet. Researchers have created a strain of the model bacterium – known as *E. coli* for short – that grows by consuming carbon dioxide instead of sugars or other organic molecules.

The achievement is a milestone, say scientists, because it drastically alters the inner workings of one of biology’s most popular model organisms. And, in the future, CO₂-eating *E. coli* could be used to make organic carbon molecules for biofuels or to produce food.

Products made in this way would have lower emissions than those made using conventional production methods, and could potentially remove the gas from the air. The work was published on 27 November (S. Gleizer *et al. Cell* **179**, 1255–1263; 2019).

“It’s like a metabolic heart transplantation,” says Tobias Erb, a biochemist and synthetic biologist at the Max Planck Institute for Terrestrial Microbiology in Marburg, Germany, who wasn’t involved in the study.

Plants and photosynthetic cyanobacteria – aquatic microbes that produce oxygen – use the energy from light to transform, or fix, CO₂ into the carbon-containing building blocks of life, including DNA, proteins and fats. But these organisms can be hard to genetically modify, which has slowed efforts to turn them into biological factories.

By contrast, *E. coli* is relatively easy to engineer, and its fast growth means that changes

“After about 200 days, cells capable of using CO₂ as their only carbon source emerged.”

can be quickly tested and tweaked to optimize genetic alterations. But the bacterium prefers to grow on sugars such as glucose – and instead of consuming CO₂, it emits the gas as waste.

Ron Milo, a systems biologist at the Weizmann Institute of Science in Rehovot, Israel, and his team have spent the past

News in focus

decade overhauling *E. coli*'s diet. In 2016, they created a strain that consumed CO₂, but the compound accounted for only a fraction of the organism's carbon intake – the rest came from an organic compound that the bacteria were fed, called pyruvate (N. Antonovsky *et al.* *Cell* **166**, 115–125; 2016).

Gas diet

In the latest work, Milo and his team used a mix of genetic engineering and laboratory evolution to create a strain of *E. coli* that can get all of its carbon from CO₂. First, they gave the bacterium genes that encode a pair of enzymes that allow photosynthetic organisms to convert CO₂ into organic carbon.

Plants and cyanobacteria power this conversion with light, but that wasn't feasible for *E. coli*. Instead, Milo's team inserted a gene that lets the bacterium glean energy from an organic molecule called formate.

Even with these additions, the bacterium refused to swap its sugar meals for CO₂. To further tweak the strain, the researchers cultured successive generations of the modified *E. coli* for a year, giving them only minute quantities of sugar, and CO₂ at concentrations about 250 times those in Earth's atmosphere.

They hoped that the bacteria would evolve mutations to adapt to this new diet. After about 200 days, the first cells capable of using



The model bacterium *Escherichia coli*.

CO₂ as their only carbon source emerged. And after 300 days, these bacteria grew faster in the lab conditions than did those that could not consume CO₂.

The CO₂-eating, or autotrophic, *E. coli* strains can still grow on sugar – and would use that source of fuel over CO₂ given the choice,

says Milo. Compared with normal *E. coli*, which can double in number every 20 minutes, the autotrophic *E. coli* are laggards, dividing every 18 hours when grown in an atmosphere that is 10% CO₂. They are not able to subsist without sugar on atmospheric levels of CO₂ – currently 0.041%.

A long way to go

Milo and his team hope to make their bacteria grow faster and live on lower levels of CO₂. They are also trying to understand how the *E. coli* evolved to eat CO₂: changes in just 11 genes seem to have allowed the switch, and researchers are now working on finding out how.

The work is a "milestone" and shows the power of melding engineering and evolution to improve natural processes, says Cheryl Kerfeld, a bioengineer at Michigan State University in East Lansing.

Researchers have already used *E. coli* to make synthetic versions of useful chemicals such as insulin and human growth hormone. Milo says that his team's work could expand the products the bacteria can make to include renewable fuels, food and other substances. But he doesn't see this happening soon.

"This is a proof-of-concept paper," agrees Erb. "It will take a couple years until we see this organism applied."

STEVE GOSCHMEISSNER/SPL

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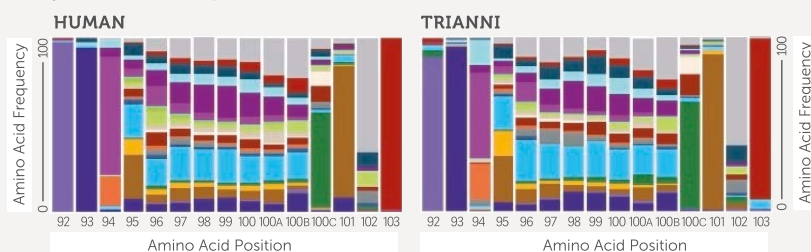
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