climate report released on 26 November warns that the Paris agreement's 2 °C goal might soon be out of reach as emissions continue to rise.

Unfinished business

At last year's conference, nations agreed on a set of rules for tracking and reporting greenhouse-gas emissions and for reviewing collective progress. However, they failed to establish clear rules for carbon markets through which emissions made in one country can be offset by investing in low-carbon technologies elsewhere. Article 6 of the Paris agreement — which aims to promote voluntary international cooperation between nations — is a central point on the agenda, and offsetting will almost certainly be discussed.

Voluntary offsetting schemes are already in use to make certain goods and services, such as passenger flights, 'carbon neutral'. Many countries, including New Zealand, Sweden and the United Kingdom, rely on offsetting to achieve their emission-reduction goals.

Critics say that offsetting schemes allow rich countries to dodge responsibility for cutting their own emissions. But a well-organized international carbon market with clear, practical rules could save up to US$250 billion in climate-mitigation costs, says Stefano De Clara, a policy adviser at the International Emissions Trading Association in Brussels. "It would engage businesses in climate action and facilitate the linkage of existing carbon pricing systems," he says. "In the end, everyone could be better off through collaboration."

Analysts have warned that poorly planned offsetting schemes could actually hinder efforts to curb global emissions. Under the Paris agreement, countries must adjust their emission-reduction pledges every five years, in line with the latest scientific evidence about what will be required to stabilize the climate. Without proper rules and bookkeeping, offsetting could simply move emission-reduction efforts around the world, instead of reducing overall emissions, says Gilles Dufrasne, an environmental economist with the Brussels-based international climate-policy watchdog Carbon Market Watch.

Jacob Werksman, a climate-policy adviser at the European Commission, warns that there are some sticking points that negotiators in Madrid might not be able to resolve. For example, some countries expect that excess carbon credits from the expiring 1997 Kyoto Protocol, the previous international climate treaty, will remain eligible for use under the Paris agreement. Such a concession would "severely undermine" the agreement, Werksman says.

This year's talks are also facing intense public scrutiny. The rapidly growing climate-protest movement is shifting the overall conversation on climate change, says Valérie Masson-Delmotte, a co-chair of the Intergovernmental Panel on Climate Change.

Politics are shifting, too. The United States' official withdrawal from the Paris agreement puts the nation in a strange position for this year's talks. It will remain a member of the UN Framework Convention on Climate Change, an international treaty under which both the Kyoto Protocol and the Paris agreement were negotiated. And US representatives will still attend future COP meetings — including next year's meeting in Glasgow, UK. But unless a future US government revokes the decision to quit the Paris agreement, the country will no longer participate in negotiations concerning the rules and implementation of the accord.

There is some hope that the European Union will provide new leadership, says Oliver Geden, a policy researcher at the German Institute for International and Security Affairs in Berlin. On 28 November, the European Parliament voted to declare a 'climate and environmental emergency', which will put pressure on EU member states to approve the European Commission's plans to cut emissions by 55% by 2030, and to achieve net-zero emissions by 2050.

"At this time it's up to the EU to demonstrate that the Paris agreement can deliver after all," says Geden. "That's a tough nut to crack."

TARGETED ATTACKS COULD MAKE BLOOD-STEM-CELL TRANSPLANTS SAFER

Such procedures show promise for genetic and immune disorders, but are currently risky.

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Physicians prepare to take a sample of a patient's bone marrow.

By Heidi Ledford

Scientists are experimenting with ways to selectively target the body's blood-making cells for destruction. Early studies in animals and people suggest that the approach could make blood-stem-cell transplants — powerful but dangerous procedures that are used mainly to treat blood cancers — safer, and thereby broaden their use. The studies come as evidence piles up that such transplants can also be used to treat some autoimmune disorders and genetic diseases.

The work, to be presented at the forthcoming annual meeting of the American Society of Hematology in Orlando, Florida, harnesses an understanding of the proteins made by different types of blood stem cell, the cells in the bone marrow that produce the various cellular components of blood.

Blood-stem-cell transplants work by replacing defective blood-making cells — which can give rise to blood cancer, as well as to genetic and autoimmune diseases — with healthy ones, either from donors or from the patients

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 scleroderma 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

Escherichia 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, CO_2-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, CO_2 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 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 CO_2, it emits the gas as waste.

"After about 200 days, cells capable of using CO_2 as their only carbon source emerged."

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