A guide to Plan B: the UK's vague strategy for post-Brexit science funding

With the United Kingdom seeming ever more likely to leave the European Union's science-funding programmes, *Nature* looks at the alternative.

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UK science minister George Freeman (left) resigned this month alongside other ministers, forcing Prime Minister Boris Johnson to step down on 7 July.

After six years of fraught negotiations, it looks increasingly likely that UK researchers will lose access to European Union research funding because of Brexit.

The loss would be crushing, leaving the EU's flagship research programme Horizon Europe, which over seven years will disburse nearly €100 billion (US$101 billion) in research funds. The UK government says that it has a back-up funding plan for researchers — called Plan B — but details are lacking, and the government is in turmoil after dozens of ministers resigned this month, forcing Prime Minister Boris Johnson to step down (Johnson has said that he will stay in the post until a successor is appointed).

In recent weeks, the European Commission (EC) has cancelled grants won by UK researchers, and the United Kingdom has set a negotiation deadline of summer's end. The failure to reach an agreement over Horizon Europe membership is the result of political differences between the United Kingdom and the EU over Northern Ireland.

With the writing now on the wall, UK-based scientists are looking for answers about what will replace the prestigious schemes that they are likely to lose access to.

Nature looks at what's known about Plan B.

Why is the United Kingdom in this position?

Since the country voted to leave the EU in 2016, its scientists have worried about the potential loss of EU research funds, a crucial income stream. Horizon Europe, which will run until 2027, includes the prestigious European Research Council (ERC), which awards unrivalled fellowships for basic research.

In 2020, a Brexit trade deal made between the United Kingdom and the EU included provisions for the United Kingdom to become an 'associate' member of Horizon Europe, which would give UK-based researchers most of the same rights to funding as scientists in EU nations. But, despite 18 months of talks on association, no deal has been inked.

Why is this coming to a head now?

Negotiations have stalled over a disagreement on how to implement a border between the Republic of Ireland, which is part of the EU, and Northern Ireland, which is part of the United Kingdom. During the negotiations, however, UK scientists were encouraged to continue bidding for EU funding in the hope that a deal would be made and funds paid.

Now, the EU has cancelled the grants of some UK scientists who had won Horizon Europe funding. Almost 150 UK-based researchers won ERC fellowships in the council's first funding call, but the EU has now said that UK researchers can take up the grants only if they transfer to an institution in an EU member country. So far, 18 scholars have opted to do so; a further 8 are waiting for transfers to be approved. The ERC has cancelled the grants of 115 previously successful applicants and a further 6 awardees have asked for more time to make a decision.

The ERC told *Nature* that it expects the number of UK-based applicants losing funds to rise, because it is offering the funds from cancelled grants to applicants on a reserve list — some of whom are in the United Kingdom and will be able to take up the grants only if they relocate.

The United Kingdom has now put pressure on the EC to make a deal. Last month, the then UK science minister George Freeman, who resigned during the effort to force Johnson to quit, said that he would give the commission until September to make a deal. Without one, the United Kingdom would enact an alternative research-funding mechanism, known as Plan B.

What is Plan B?

Plan B is the UK government's alternative to associating with Horizon Europe (which has always been the first choice, or Plan A). Ministers have been seriously considering an alternative to association since 2019. A report that year called for the creation of a flagship fellowship programme to rival the ERC's, as well as a suite of international fellowships to lure talent from overseas and a boost to basic-research funding.

Last month, Freeman gave evidence to a parliamentary science committee about how the plan is shaping up. He described a four-pillar programme that included a "very strong talent piece" that would offer fellowships and international fellowships. A second pillar, combining industry and innovation, would provide a "bold offer" to break the cycle of short-term funding; he described this as "a DARPA-style, Wellcome Trust-style, Max Planck-style funding mechanism".

A third global pillar would look to "deepen

our multilateral and bilateral work across the world to tackle global challenges". A final pillar would cover major investments in infrastructure.

Plan A is still the best outcome for UK scientists, but it's right that the government is making alternative plans, says Stephanie Smith, head of research policy at the Russell Group of UK research universities. "It's time the details were published so the UK research community can make the most of Plan B if it is required," she adds. "We would need an exciting and compelling offer on talent, on innovation and global partnerships to ensure we can deliver on ambitions to maintain and strengthen the UK's position as a science superpower."

Who would be in charge of Plan B?

This is not yet clear. The central research funder UK Research and Innovation (UKRI) could be an option. It already disburses around £8 billion of research funding annually (UKRI declined *Nature*'s request for comment on Plan B). The government ministry responsible for science — the Department for Business, Energy & Industrial Strategy — said that details of its "immediate plans" will be published shortly.

News reports have suggested that the UK government has approached the country's four national academies to run fellowship schemes, but that no decision has been made. The academies — the Royal Academy of Engineering, the Royal Society, the Academy of Medical Sciences and the British Academy — declined *Nature*'s requests for comment on specific plans.

A Royal Society spokesperson said that the society has contributed to the government's contingency planning, but that its position remains that association with Horizon Europe is the best option for UK science.

Where's the money coming from?

In 2021, the UK Treasury put aside £6.9 billion to foot the bill of associating with Horizon Europe and other EU science programmes, or to fund any domestic alternative, until 2024–25. Speaking to the science committee in June, Freeman said that negotiations with the treasury about how to allocate the funding for such a scheme were ongoing.

By Holly Else

News explainer

CRISPR COUSIN TESTED IN LANDMARK HEART-DISEASE TRIAL

Gene-therapy trial launches pivotal year for precise genome-editing technique known as base editing.

By Heidi Ledford

It's test time for CRISPR's cousin.

A clinical trial that recently treated its first participant will test whether base editing — a genome-editing method related to the CRISPR–Cas9 system — can safely be used to make precise, single-letter changes to a DNA sequence in a cholesterol-regulating gene without breaking both strands of DNA first, as CRISPR–Cas9 would do.

This study will be followed by another base-editing trial, slated to treat its first participant later this year, that will aim to tackle sickle-cell disease, a genetic blood disorder.

Both tests are expected to report results in 2023, and further base-editing treatments are working their way through the pipeline towards clinical trials. "It's very exciting that the first clinical trials are starting," says Gerald Schwank, who studies the use of genome editing to treat diseases at the University of Zurich, Switzerland. "We've got a lot to learn."

In CRISPR–Cas9 genome editing, the Cas9 enzyme breaks both strands of DNA at the site that is to be edited. The cell's DNA-repair processes stitch the strands back together, but sometimes make mistakes. This means that a range of DNA sequence changes are possible.

Base editing, by contrast, avoids cutting both strands of the DNA by coupling a Cas9 protein that cuts only one strand of DNA, rather than both, to another enzyme that chemically converts one DNA letter to another. The Cas9 directs the base-editing enzyme to the right location in the genome; the other enzyme then acts on that site, ideally producing only one edit.

This level of precision has spurred hopes that the technique could provide safer and more controllable therapies for genetic diseases than is possible with CRISPR–Cas9.

The first trial will use a base editor to convert an adenine base (A) to a guanine one (G) in the DNA encoding a protein called PCSK9, a key regulator of blood cholesterol levels. The approach, developed by Verve Therapeutics in Cambridge, Massachusetts, aims to reduce the amount of functional PCSK9 in people with a condition called heterozygous familial hypercholesterolaemia, which causes high cholesterol and can lead to heart disease. Disabling PCSK9 has been shown to reduce cholesterol levels and cut the risk of heart disease, and several therapies already on the market reduce PCSK9 activity.

"It could be very promising," says Piter Bosma, who studies liver diseases at the Amsterdam University Medical Centers. Bosma points to preclinical results in macaques (*Macaca fascicularis*) published last year, which showed that the treatment reduced blood levels of PCSK9 by 81% and lowered blood cholesterol levels without harmful side effects (K. Musunuru *et al*. *Nature* **593**, 429–434; 2021). Another study in macaques by Schwank and his colleagues also found that the treatment was safe (T. Rothgangl *et al*. *Nature Biotechnol*. **39**, 949–957; 2021).

Although cautiously optimistic, researchers will be looking to see whether the treatment introduces any off-target genetic changes. The risk of these side effects might be balanced by the benefit of treatment for people with high cholesterol, but researchers will need long-term safety data before feeling assured that the treatment can be used more widely.

The Verve trial aims to edit cells directly in the body. The team has encased the base-editing components — messenger RNA encoding the enzyme needed to alter DNA, and an extra snippet of RNA that will direct the enzymes to the correct location — in lipid nanoparticles, similar to those used in mRNA COVID-19 vaccines. The nanoparticles will be concentrated in the liver, a key site of PCSK9 production.

By contrast, the upcoming sickle-cell trial will use base editing to alter DNA in blood stem cells that have been removed from the body. The edited cells will then be reinfused into participants. The trial will be conducted by Beam Therapeutics, also based in Cambridge, which collaborated with Verve to develop the cholesterol base-editing therapy.

Similar therapies are being developed to treat conditions such as leukaemia; a rare metabolic condition called glycogen storage disease; and Stargardt's disease, which can cause blindness. And other CRISPR-derived approaches are being readied for their own foray into the clinic. Alternative Cas enzymes have been discovered that can edit RNA rather than DNA. Schwank says that his laboratory has mostly moved on from base editing, to a technique called prime editing, which offers more precision: "It's all moving fast."