

sequence of a short fragment of RNA, called a guide RNA. In many organisms, these DNA breaks are then repaired by the cell in ways that can alter the original DNA sequence.

### SLICE AND DICE

Liu and his colleague, chemist Weixin Tang, also at the Broad Institute, took advantage of Cas9's DNA-slicing ability to engineer a cellular recorder using circular molecules of DNA called plasmids. Plasmids replicate inside bacterial cells, sometimes producing hundreds of copies in a single cell.

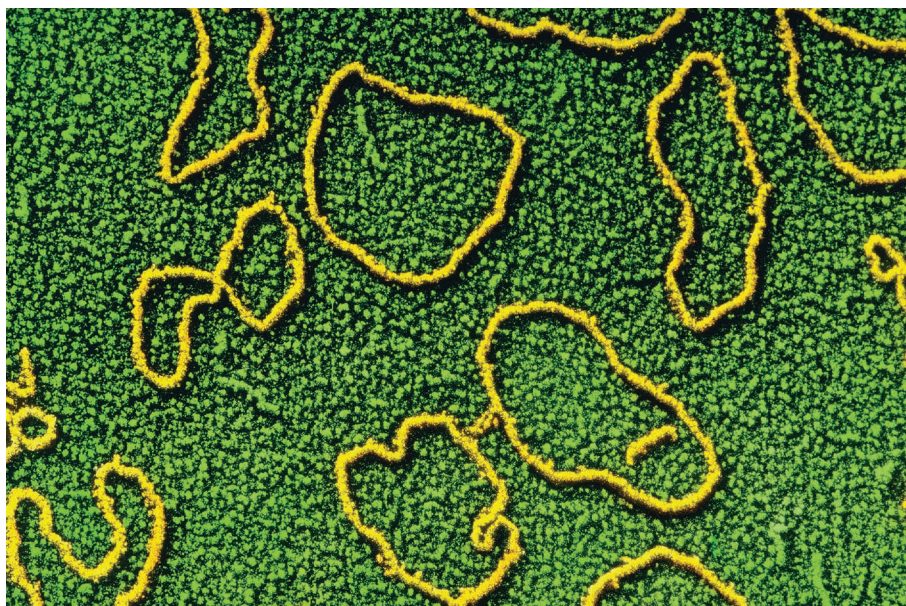
Liu and Tang altered three DNA letters in one such plasmid, so that it contained a sequence targeted by a guide RNA. They also engineered a bacterium to express Cas9 only in the presence of a particular antibiotic, and dubbed the whole system CAMERA1.

Bacteria lack some of the DNA-repair mechanisms used by mammalian cells to fix the damage wrought by Cas9 — instead, when the plasmid is targeted by Cas9, it is degraded. Another plasmid then replicates to take the place of the lost one.

Liu and Tang put both the altered and normal plasmids into cells and measured the relative ratio of the two. The proportion of altered plasmid fell in cells that had been treated with antibiotic, because the cells had begun to degrade the altered plasmids.

The result was an unusually sensitive recorder: Liu and Tang could read out information from as few as ten bacterial cells. The magnitude of the change reflected the amount of antibiotic present, or the duration of exposure. Liu and Tang also developed methods for resetting the ratio of altered to unaltered plasmid, erasing the first recording and readying the cell to document the next event using the same set of plasmids.

They then moved on to create more



Circular DNA molecules called plasmids have been transformed into cellular-data recorders.

recorders. One, called CAMERA2, relies on modified CRISPR systems called base editors, developed by Liu's lab<sup>4</sup> in 2016, that can alter single DNA letters in the genome without relying on the cell's DNA-repair mechanisms. Liu and Tang used CAMERA2 to record up to four different stimuli in bacterial cells, including exposure to light and viruses, and the order in which the stimuli occurred.

The researchers also modified CAMERA2 to work in mammalian cells, recording changes directly in the genome rather than in plasmids. Tang and her colleagues hope to use the system to answer questions about how cells take on specific identities.

The CAMERA recorders will join a host of other cellular recorders under development. Synthetic biologist Harris Wang of Columbia

University Medical Center in New York City has been developing systems that he hopes to use to study microbes in the gut<sup>5</sup>.

And Junker's lab is working on a recorder to trace the developmental pathway of individual cells in zebrafish. He first thought of the approach a little over two years ago, he says. "I thought this was an exotic idea that I had," says Junker. "And suddenly everybody is doing it." ■

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2. Chen, J. S. *et al.* *Science* <http://dx.doi.org/10.1126/science.aar6245> (2018).
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4. Komor, A. C. *et al.* *Nature* **533**, 420–424 (2016).
5. Sheth, R. U., Yim, S. S., Wu, F. L. & Wang, H. H. *Science* <http://dx.doi.org/10.1126/science.aao0958> (2017).

### FUNDING

# Indonesian funding agency short on cash

*First dedicated fund has failed to raise enough money to finance projects.*

BY DYNA ROCHMYANINGSIH

Indonesian scientists expecting to receive hundreds of thousands of dollars for research are stuck in limbo because the country's first dedicated science-funding agency is struggling to raise enough money.

After years of insufficient research funding, scientists were delighted when the Indonesian Science Fund (ISF) launched, in March 2016. Its aim was to boost investment in research and improve research quality. The following May, it opened up applications for grants worth up to 1.5 billion rupiah (US\$110,000) a year for

3 years. Scientists submitted 467 proposals.

Almost 18 months later, the ISF, which is managed by the Indonesian Academy of Sciences in Jakarta, says it has selected 10 projects that deserve to be funded, but does not have the money to give to researchers.

"The delay from ISF is very disappointing," says a researcher in Jakarta who was told in February 2017 that their application might be accepted, but was asked to revise their project budget. The scientist, who asked to remain anonymous for fear of jeopardizing the payment, says that they have not heard from the ISF since. "I am trying to find international research funding. But as long as we don't get any official rejection from ISF, it is unethical for us to send [our] research proposal to other funding agencies," they say. "In this situation, scientists are the victims."

Although the ISF seeks funds from a range of sources, including philanthropy and ▶



DARREN WHITESIDE/REUTERS

Indonesian scientists were hopeful a dedicated fund would reverse years of insufficient investment.

▶ foreign donors, the Indonesian government committed US\$3 million to the agency in its first year, through the finance ministry's Indonesia Endowment Fund for Education. The endowment fund also signed a memorandum of understanding with the ISF, agreeing to give the agency money for five years.

Teguh Rahardjo, the ISF's executive director, says that the agency has received some of this cash, but not enough to support all of its grant programmes. Government budget constraints have contributed to the funding shortfall, and the agency is now searching for other sources of money, he says.

He says that the ISF was able to contribute 12 billion rupiah this year towards research grants for collaborations between Indonesian and UK universities. The programme is also supported by the Newton Fund, a British research-development group.

Indonesian researchers have typically had to rely on yearly funding from the national budget, which invests only 0.08% of the country's gross domestic product in scientific research each year. Some scientists argue that the process by which this money is awarded to universities or research centres by various ministries, including the Ministry of Research,

Technology and Higher Education, isn't open and transparent. Syarif Hidayat, head of legal, cooperation and information services at the ministry, denies that the funding process is not open and says the ministry is working on ways to stretch research funding over multiple years.

The ISF was established to support long-term research. It is inspired by funding agencies such as the US National Science Foundation, and uses independent peer review to award funding.

"It is very unfortunate that ISF postpones this grant," says molecular biologist Riza Putranto at the Indonesian Research Institute for Biotechnology and Bioindustry in Bogor. "We cannot rely on national budget alone to conduct high-quality research in Indonesia," says Putranto, whose ISF funding application was not successful.

The Ministry of Finance did not respond to *Nature's* questions about budget constraints. ■

#### CORRECTION

The Editorial 'Restore justice in Turkey' (*Nature* **554**, 145; 2018) stated that the text-messaging system ByLock was available only through personal introduction. In fact, it was widely available and could have been downloaded by anyone.