REVERSAL OF BIOLOGICAL CLOCK RESTORES VISION IN OLD MICE

'Reprogramming' approach seems to make old cells young again.

By Heidi Ledford

Researchers have restored vision in old mice and in mice with damaged retinal nerves by resetting some of the thousands of chemical marks that accumulate on DNA as cells age. The work, published on 2 December in *Nature*, suggests a new approach to reversing age-related decline, by reprogramming some cells to a 'younger' state in which they are better able to repair or replace damaged tissue.

"It is a major landmark," says Juan Carlos Izpisua Belmonte, a developmental biologist at the Salk Institute for Biological Studies in La Jolla, California, who was not involved in the study. "These results clearly show that tissue regeneration in mammals can be enhanced."

Visionary approach

Ageing affects the body in myriad ways — among them, adding, removing or altering chemical groups such as methyls on DNA. These 'epigenetic' changes accumulate as a person ages, and some researchers have proposed tracking the changes as a way of calibrating a molecular clock to measure biological age, an assessment that takes into account biological wear-and-tear and can differ from chronological age.

"We set out with a question: if epigenetic changes are a driver of ageing, can you reset the epigenome?" says David Sinclair, a geneticist at Harvard Medical School in Boston, Massachusetts, and a co-author of the *Nature* study (Y. Lu *et al*. *Nature* **588**, 124–129; 2020). "Can you reverse the clock?"

There were suggestions that the approach could work: in 2016, Belmonte and his colleagues reported the effects of expressing four genes in mice genetically engineered to age more rapidly than normal (A. Ocampo *et al*. *Cell* **167**, 1719–1733; 2016). It was already known that triggering these genes could cause cells to lose their developmental identity — the features that make, for example, a skin cell look and behave like a skin cell. But rather than turn the genes on and leave them that way, Belmonte's team turned them on for only a few days, then switched them off again. The result was mice that aged more slowly, and had a pattern of epigenetic marks indicative of younger animals. But the technique had disadvantages: previous work had shown that if the genes are present in extra copies or expressed for too long, some mice will develop tumours.

In Sinclair's lab, geneticist Yuancheng Lu looked for a safer approach. He dropped one of the four genes used by Belmonte's team — one that is linked to cancer — and put the remaining three into a virus that could shuttle them into cells. He included a switch that would allow him to turn the genes on by giving mice water spiked with a drug. Withholding the drug would switch the genes off again.

Because mammals lose the ability to regenerate components of the central nervous system early in development, Lu and his colleagues tested their approach there — in the eye's retinal nerves. They first injected the virus into the eye to see whether expression of the three genes would allow mice to regenerate injured nerves — something that no treatment had yet been shown to do.

Lu remembers the first time that he saw a nerve regenerating from injured eye cells. "It was breathtaking," he says.

> **"If epigenetic changes are a driver of ageing, can you reset the epigenome? Can you reverse the clock?"**

The team went on to show that its system improved visual acuity in mice with age-related vision loss, or with increased pressure inside the eye — a hallmark of the disease glaucoma. The approach also reset epigenetic patterns to a more youthful state in mice and in human cells grown in the laboratory. It is still unclear how cells preserve a memory of a more youthful epigenetic state, says Sinclair, but he and his colleagues are trying to find out.

In the meantime, Harvard has licensed the technology to Boston company Life Biosciences, which, Sinclair says, is carrying out preclinical safety assessments with a view to developing it for use in people. It would be an innovative approach to treating vision loss, says Botond Roska, director of the Institute of Molecular and Clinical Ophthalmology in Basel, Switzerland, but will probably need considerable refinement before it can be deployed safely in humans.

Q&A

How sex and gender analysis improves science

The European Commission has said that it aims to make sex and gender analysis mandatory in the research it funds through its €85-billion (US$100-billion) Horizon Europe programme. The strengthened policy is a result of recommendations made in a report (see go.nature.com/3mryv1a), produced last month by an expert group chaired by Londa Schiebinger, who studies gender and science at Stanford University in California. *Nature* spoke to Schiebinger about the group's work.

How do you convince people of the need for sex and gender analysis in research?
Our iconic example of failure when you don't do this analysis is that between 1997 and 2001, ten prescription drugs were withdrawn from the US market, eight of which were more dangerous for women than for men. When drugs fail, you're losing money and people are suffering and dying. From preclinical studies to human clinical trials, you have to collect data on males and females and analyse them separately.

What mistakes do researchers make in these analyses?
The biggest mistake is simply ignoring sex, gender and intersectionality. Another is to not distinguish between biological sex and sociocultural gender. Gender is specific to ethnicity, age and culture. Researchers need to get the right variables, collect their data correctly and do the analysis well.

Are there research areas where people might be surprised that sex and gender analysis is essential?
For some marine organisms, sex is determined by temperature. Our report includes a fascinating study from Australia, where they found that the turtles in the north of the Great Barrier Reef were 99% female, whereas in the cooler south, it was about 67% female. It's important that we understand how global warming is skewing these ratios, so that we can efficiently manage ecosystems.

Interview by Elizabeth Gibney.
Edited for length and clarity.