Move over CRISPR

Will epigenome editing be able to aid medical treatment by altering cells or altogether prevent diseases? **Emily Baumgaertner Nunn** interviews those in the know

It is one of biology's most ingenious rhythms — every baby is born young. No matter how much wear and tear their parents' DNA accumulated over their lifetimes, reproduction erases the molecular scars, handing a clean slate to the next generation.

Now, a new frontier in biotechnology aims to harness this natural mechanism to do something once thought impossible: scrub away the biological detritus of our own past. By mimicking Mother Nature's magic eraser, geneticists are working to open a new avenue for treating or preventing disease later in life — not by editing genes themselves but by altering when, where and how genes are expressed.

All of this is possible thanks to the epigenome, a network of chemical tags throughout the body that latch on to DNA and tell each cell type how to behave. If a person's DNA is a string of notes in a musical score, the epigenome is the collection of the conductor's pencil markings left on the page — accumulated through experience over time, indicating which notes to play louder or softer or to skip entirely.

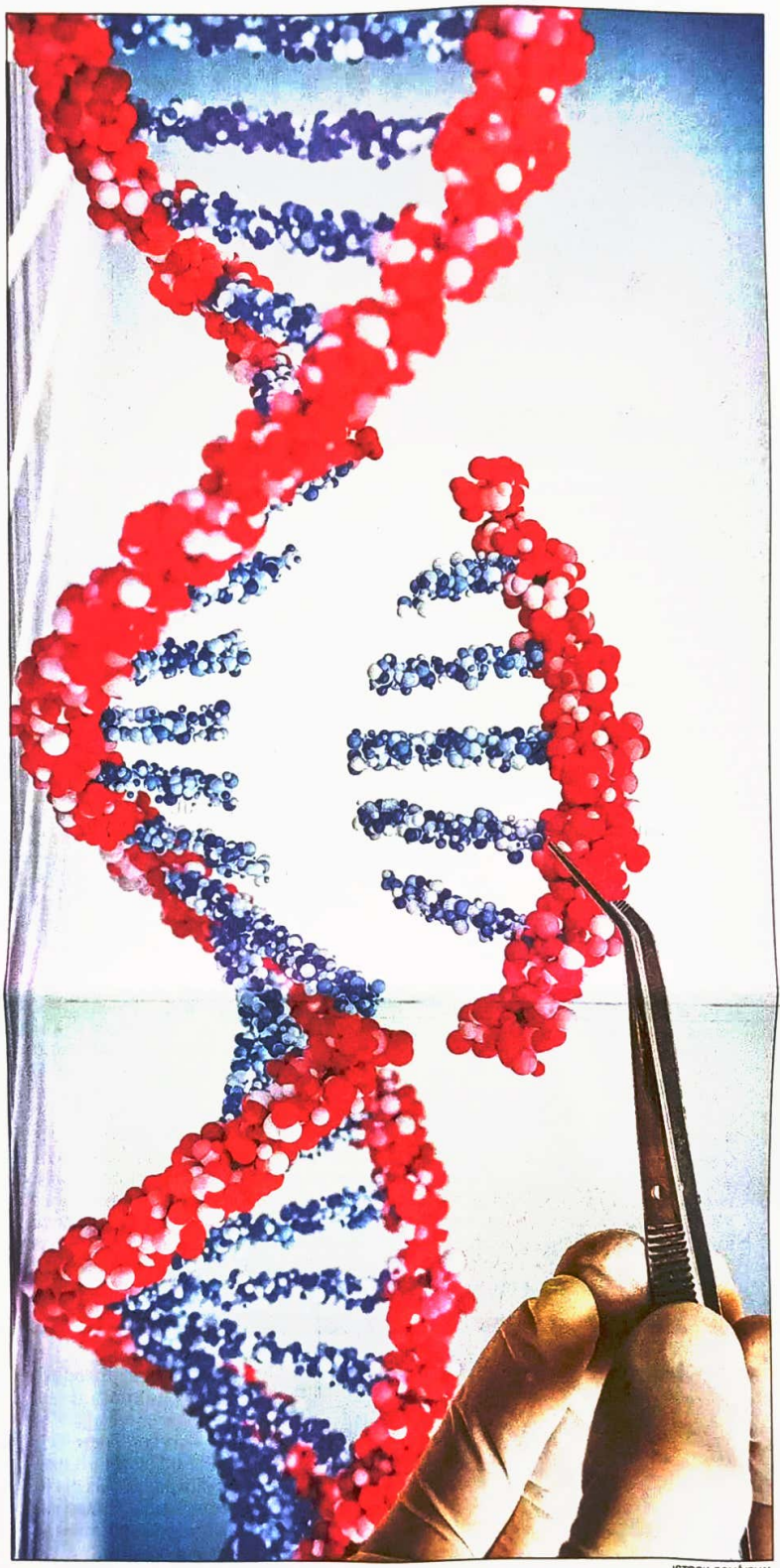
Unlike the fixed genome, the epigenome changes, responding to external factors such as chronic stress, poor diet, exposure to toxins or infections, and simple ageing. For example, blood cells in a child exposed to secondhand smoke might dial up genes that trigger inflammation and dial down those for cellular repair, increasing the child's long-term risk of asthma, cardiovascular disease and cancer.

Existing gene-editing tools can permanently rewrite the genetic code that underlies our "nature". But the new approach, called epigenome editing, strives to edit the buildup of "nurture" in our cells instead.

"There is no question that our environmental exposures change what our genes do," said Fyodor Urnov, a gene-editing expert and the director of therapeutic research and development at the Innovative Genomics Institute at the University of California, Berkeley, US. He is a co-founder of Tune Therapeutics, a company that is running clinical trials for an epigenome editing tool to treat chronic hepatitis B in the liver.

The treatment works by silencing virus DNA within the liver cell, preventing it from producing proteins that keep the immune system at bay and allowing the body to finally clear the infection.

"Our genes learn from experience — that's nurture," Urnov said. "So epigenome editing is a way to reverse the nurture."



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At least 12 companies are already experimenting with the technique, and several have moved their tools into clinical trials. In May, Tune Therapeutics reported early data showing that high doses of their drug significantly reduced hepatitis B markers in some participants.

Epigenome editing is also uniquely suited for scenarios in which doctors don't want to break a gene or slice it out of the genome entirely, but instead aim to tune its expression up or down appropriately. Consider people who suffer from chronic pain, for example, and who need the dial spun way down — but not off entirely. A total insensitivity to pain puts people at risk of serious harm, since they may not notice broken bones or deep burns.

"You want that Goldilocks volume of gene behaviour: not too much or little, but just right," Urnov said.

Gene editing with CRISPR, which snips the DNA itself, has been reserved mostly for devastating disorders such as sickle cell disease because the risks of a mistake — like accidentally deleting vital code — often outweighed the rewards.

Some groups have begun experimenting with CRISPR-based tools to treat common conditions such as high cholesterol, but the option of epigenome editing could provide a safer alternative. Rather than taking a daily statin, some patients might soon be able to receive a single injection from Scribe Therapeutics, which would silence a gene in the liver that destroys receptors responsible for clearing LDL cholesterol, drastically lowering their risk of heart disease.

"This is sort of the ultimate one-and-done treatment," said Jonathan Weissman, a biologist at the Massachusetts Institute of Technology in the US, and a co-founder of nChroma Bio, another genetic medicines company working on chronic hepatitis B.

Because epigenome editing so far appears safe and potentially reversible, some scientists wonder whether the technology will be used in nonmedical and cosmetic contexts. Weissman said the editing could perhaps boost growth hormone levels to make a child grow taller or to cultivate more cells in the cerebral cortex, strengthening memory or intelligence. He also envisioned professional athletes using it to temporarily ramp up natural hormones that can give them a competitive edge.

"I don't think we know enough to be able to do it at the moment but it is not far off from what's imaginable," he said. Still, he added, "I think that there's a lot of good we can do before we start worrying about the bad."

Hank Greely, a law professor at Stanford University, US, who specialises in the ethical implications of new biotechnologies, is also not particularly concerned about the future of epigenome editing beyond issues of safety, effectiveness and access. To him, the tools may be novel, but the idea of adjusting our epigenomes is not particularly new.

"We modify nurture all the time," he said, from taking Ozempic to reading self-help books, hoping to affect the nexus where environment and biology meet. "Now that we're directly looking at the epigenetics, it feels different," he said, "but we're actually seeing what's been under the hood the entire time."

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