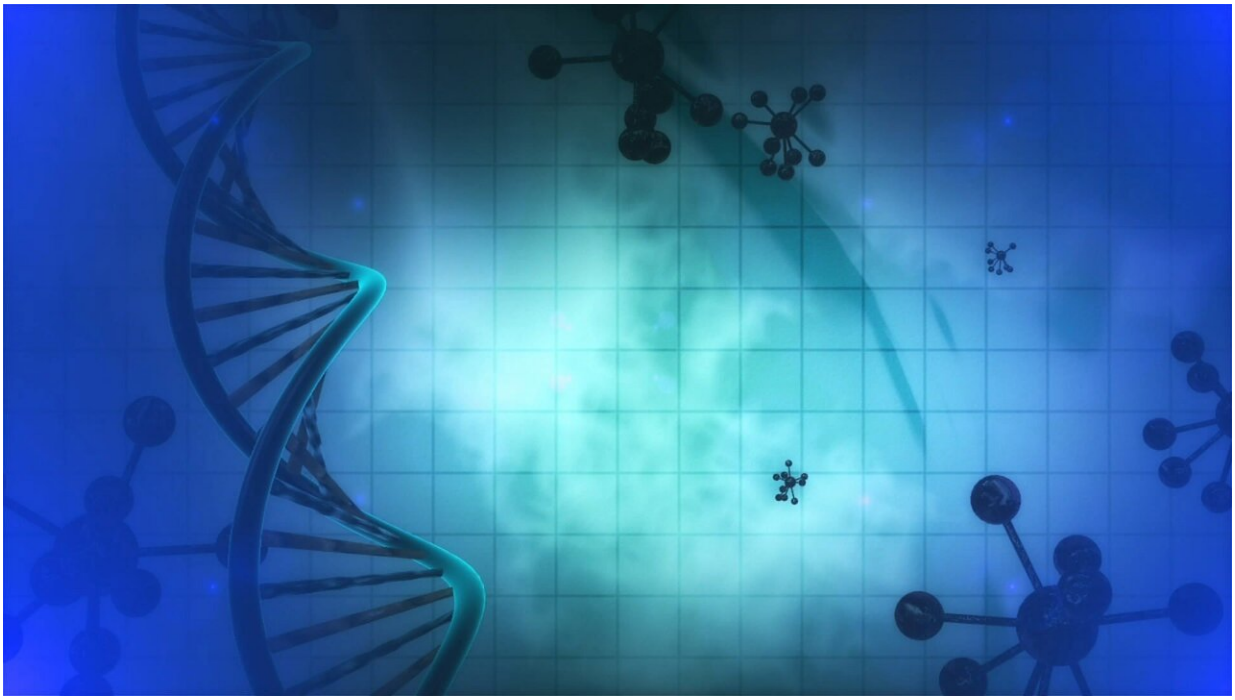
New AI tool makes speedy gene-editing possible

January 26 2023



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An artificial intelligence program may enable the first simple production of customizable proteins called zinc fingers to treat diseases by turning genes on and off.

The researchers at NYU Grossman School of Medicine and the University of Toronto who designed the tool say it promises to accelerate

the development of gene therapies on a large scale.

Illnesses including cystic fibrosis, Tay-Sachs disease, and sickle cell anemia are caused by errors in the order of DNA letters that encode the operating instructions for every human cell. Scientists can in some cases correct these mistakes with gene editing methods that rearrange these letters.

Other conditions are caused, not by a mistake in the code itself, but by problems in how the cellular machinery reads DNA (epigenetics). A gene, which provides the recipe for a particular protein, often partners with molecules called transcription factors that tell the cell how much of that protein to make. When this process goes awry, over- or underactive genes contribute to diabetes, cancer, and neurological disorders. As a result, researchers have been exploring ways to restore normal epigenetic activity.

One such technique is zinc-finger editing, which can both change and control genes. Among the most abundant protein structures in the human body, zinc fingers can guide DNA repair by grabbing onto scissor-like enzymes and directing them to cut faulty segments out of the code.

Similarly, zinc fingers can also hook onto transcription factors and pull them toward a gene segment in need of regulation. By customizing these instructions, genetic engineers can tailor any gene's activity. A drawback, however, is that artificial zinc fingers are challenging to design for a specific task. Since these proteins attach to DNA in complex groups, researchers would need to be able to tell—out of countless possible combinations—how every zinc finger interacts with its neighbor for each desired genetic change.

The study authors' new technology, called ZFDesign, overcomes this obstacle by using artificial intelligence (AI) to model and design these

interactions. The model is based on data generated by the screen of nearly 50 billion possible zinc finger-DNA interactions in the researchers' labs. A report on the tool is publishing online Jan. 26 in the journal *Nature Biotechnology*.

"Our program can identify the right grouping of zinc fingers for any modification, making this type of gene editing faster than ever before," says study lead author David Ichikawa, Ph.D., a former graduate student at NYU Langone Health.

Ichikawa notes that zinc-finger editing offers a potentially safer alternative to CRISPR, a key gene-editing technology with applications that range from finding new ways to kill cancer cells to designing more nourishing crops. Unlike the entirely human-derived zinc fingers, CRISPR, which stands for clustered regularly interspaced short palindromic repeat, relies on bacterial proteins to interact with genetic code. These "foreign" proteins could trigger patients' immune defense systems, which may attack them like any other infection and lead to dangerous inflammation.

The study authors add that besides posing a lower immune risk, the small size of zinc-finger tools may also provide more flexible gene therapy techniques compared with CRISPR by enabling more ways to deliver the tools to the right cells in patients.

"By speeding up zinc-finger design coupled with their smaller size, our system paves the way for using these proteins to control multiple genes at the same time," says study senior author Marcus Noyes, Ph.D. "In the future, this approach may help correct diseases that have multiple genetic causes, such as heart disease, obesity, and many cases of autism."

To test the computer's AI design code, Noyes and his team used a customized zinc finger to disrupt the coding sequence of a gene in

human cells. In addition, they built several zinc fingers that successfully reprogrammed transcription factors to bind near a target gene sequence and turn up or down its expression, demonstrating that their technology can be used for epigenetic changes.

Noyes, an assistant professor in the Department of Biochemistry and Molecular Pharmacology at NYU Langone, cautions that, while promising, zinc fingers can be difficult to control. Since they are not always specific to a single gene, some combinations can affect DNA sequences beyond a particular target, leading to unintended changes in genetic code.

As a result, Noyes says the team next plans to refine their AI program so it can build more precise zinc-finger groupings that only prompt the desired edit. Noyes is also a member of NYU Langone's Institute for System Genetics.

More information: Philip Kim, A universal deep-learning model for zinc finger design enables transcription factor reprogramming, *Nature Biotechnology* (2023). DOI: 10.1038/s41587-022-01624-4.
www.nature.com/articles/s41587-022-01624-4

Provided by NYU Langone Health