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Genome editing aims to snip viruses out of existence

TOMOYUKI ENDO and TAKURO KUSASHIO, Nikkei staff writers

At the first meeting of the Japanese Society for Genome Editing, in Hiroshima, many researchers reported on medical applications for the technology.

TOKYO Armed with a pair of "molecular scissors," scientists in the field of genome editing may finally be closing in on cures for diseases like hepatitis B and AIDS.

Like other viral diseases, hepatitis B and AIDS result from viruses that infect cells and hijack the genetic machinery to replicate their own DNA. Although management of both diseases is possible using antiviral medications, eliminating their DNA from the body is difficult. Lying dormant in the nucleus of cells, viral DNA can be triggered back into replication at any time. To tackle this challenge, teams in Japan and

elsewhere are looking to genome editing, a promising new approach aimed at snipping viral DNA right out of existence.

SAVING THE LIVER Hepatitis B causes cirrhosis of the liver and liver cancer. The hepatitis B virus, or HBV, infects liver cells and deposits its DNA into the cell nucleus, where it resides separately from the chromosomes and replicates independently.

Associate professor Yumi Kanegae of the Jikei University School of Medicine is collaborating with the University of Tokyo to eliminate this DNA from liver cells using a genome editing method known as CRISPR/Cas9.

To slice up genes in the desired location, the CRISPR/Cas9 system uses the Cas9 enzyme as a pair of molecular scissors, directed to the cutting site by a short strand of RNA dubbed a guide RNA.

Cas9 cuts the DNA wherever the guide RNA has attached. Kanegae's strategy is to develop different guide RNAs that attach to different places along the HBV DNA and introduce them into infected cells simultaneously. The idea is to cut the viral DNA into numerous pieces so that it becomes fragmented and ineffective.

In experiments using cultured human liver cells infected with HBV, Kanegae's team used a set of three different guide RNAs and succeeded in eliminating 90% of the viral DNA from the cells.

EXCISING AIDS HIV, the virus that causes AIDS, is what a Kyoto University team led by professor Yoshio Koyanagi has put in the crosshairs of their genome-editing efforts.

HIV infects white blood cells and integrates its DNA directly into that of the cells, making it very difficult to completely eliminate the virus from the body.

The Koyanagi team is gunning for HIV using a genome editing method called TALEN. They have developed a nuclease reagent that cuts out the HIV DNA by snipping it free at both ends.

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In experiments using cultured white blood cells, this method proved capable of eliminating 80% of all HIV DNA from infected cells.

Elsewhere in the world, an HIV therapy using genome editing has already reached the clinical testing stage. Rather than cutting out the HIV DNA, this therapy seeks to close the "cellular door" the virus uses for infection. The white blood cells are removed from the patient, genome editing is used to eliminate the protein that serves as the viral entranceway, and then the cells are returned.

However, Koyanagi sees a weakness in this strategy. "To completely cure the patient of HIV, you would need to remove the virus from the bone marrow, which is where white blood cells are made, and that is not easy."

Koyanagi's team has also demonstrated the effectiveness of the CRISPR/Cas9 system against HIV, but the viral DNA cannot be completely eliminated this way.

"A cure with genome editing alone would be difficult to achieve at this point," Koyanagi acknowledged.

Instead, he envisions a two-step process, first using existing antiviral medications to reduce the HIV load, and then snipping away with genome editing.

Kanegae has a similarly realistic assessment about her fight against HBV. "The complete elimination of the HBV DNA is not at hand."

One great challenge is getting the nuclease reagents that function as molecular scissors into all of the cells infected by the virus. To treat HBV, a way must be developed to direct the injected reagent efficiently to the targeted liver cells and ensure it affects only those cells.

In order for HBV to proliferate, its DNA must be transcribed into RNA, because it is only from RNA that the viral genes can be expressed. That has led scientists like Kanegae to propose a combination strategy,

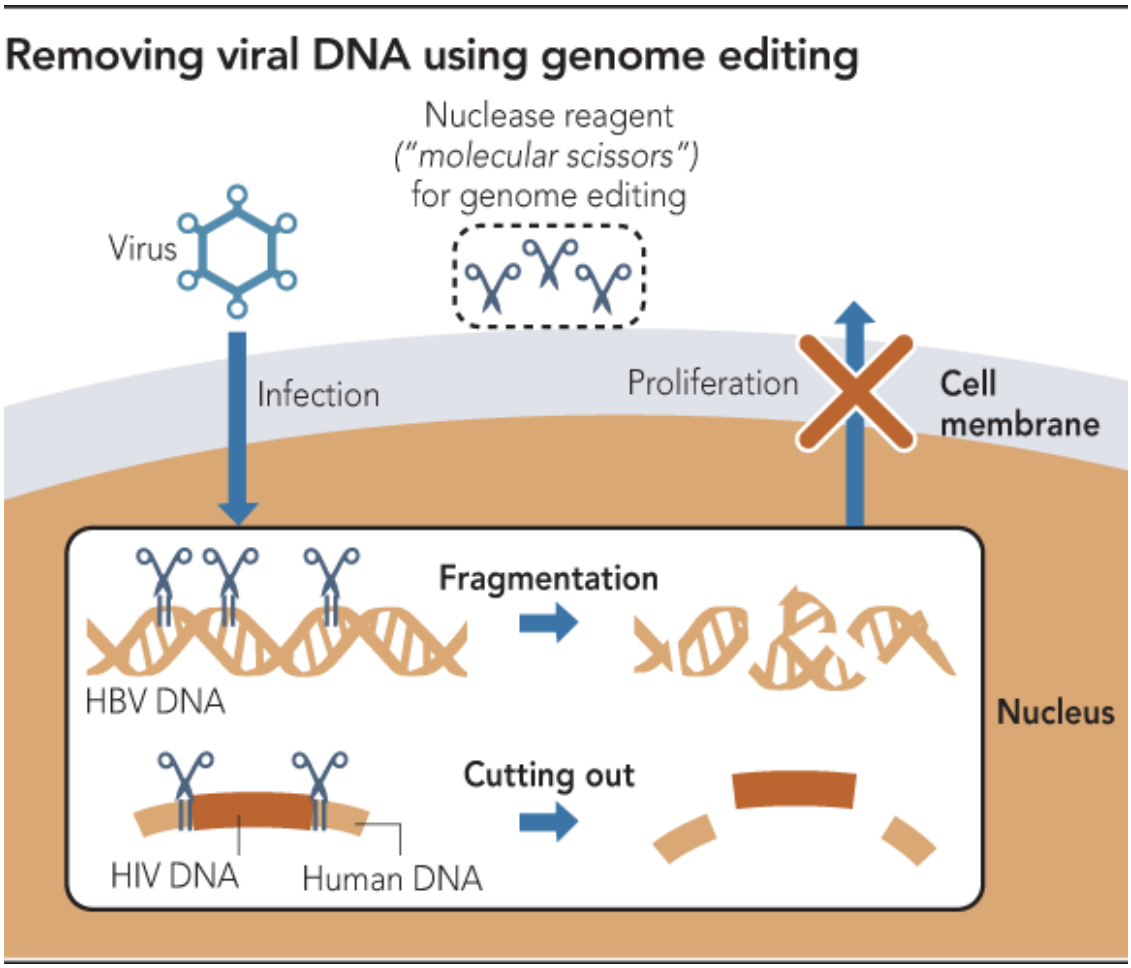
coupling genome editing, which targets the DNA in the nucleus, with other methods that target the destruction of RNA.

Both Kanegae's team and Koyanagi's plan to conduct animal experiments to test the efficacy of their genome editing techniques against HBV and HIV.

For this, the teams plan to use "humanized" mice that have been genetically engineered to carry human liver cells or human white blood cells.

Eliminating HBV and HIV through genome editing would spare patients costly and prolonged regimens of antiviral medications.

Genome editing has already become a hot topic in the agriculture and fisheries industries, and a recent academic conference in Japan underscored the rapid growth of interest in the technology well beyond these fields.



Much of the research at the first conference of the Japanese Society for Genome Editing, held in Hiroshima in early September, focused on medical and health care applications.

A team led by Satoshi Gojo, a professor at the Kyoto Prefectural University of Medicine, reported that they were able to use CRISPR/Cas9 to repair the gene that causes Fabry disease, which weakens the function of the heart.

Fabry disease is caused by an enzyme deficiency due to a mutation in the gene that controls the enzyme. This results in a failure to metabolize lipids, which then build up to harmful levels, resulting in a variety of symptoms.

A group of researchers led by Takayuki Miyazawa, an associate professor at Kyoto University's Institute for Virus Research, has successfully used genome-editing technology to remove the genes of viruses from the DNA of cells used to produce animal vaccines.

Animal cells generally contain many genes of viruses that have been incorporated into their DNA over the course of evolution. Miyazawa's team has managed to eliminate these genes, removing the risk of viruses entering vaccines made from such cells.

The researchers said they hope to use the same method to remove viral genes from the cells of chicken eggs used to produce vaccines for human use.

But the ethical issues thrown up by the editing of human DNA cannot be ignored. Last year, for example, a group of Chinese researchers used the CRISPR/Cas9 technique to edit the genomes of human embryos, provoking controversy in the scientific community.

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