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SingpaoreÃ?Â researchers create AI-guided gene-editing tool for precise and safer DNA correction

March 18, 2026 | News | By Hithaishi C Bhaskar

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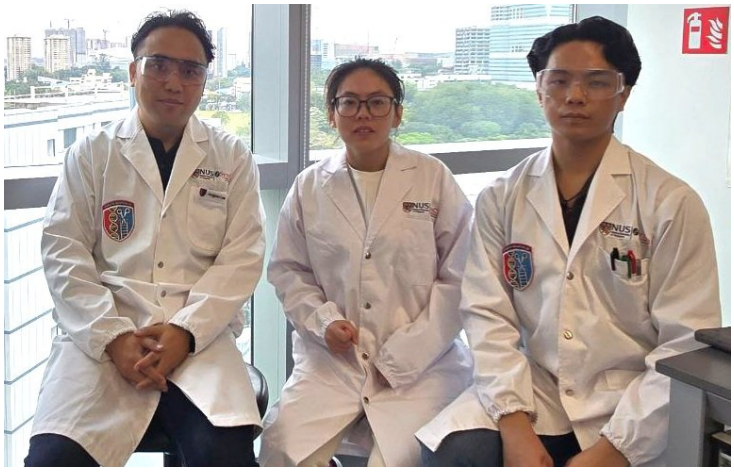

Researchers at Singapore's NUS Medicine have developed a method to enhance compact gene-editing tools called **base editors**, which correct single-letter DNA mutations without fully cutting the DNA, potentially making them safer for gene therapies.

Base editors are powerful for treating inherited diseases but are often too large for delivery systems like adeno-associated viruses (AAVs) used in therapy. Additionally, improving their efficiency can increase the risk of unintended DNA damage and toxicity.

Study was led by Assistant Professor Jungjoon K. Lee, from the Department of Biochemistry, Synthetic Biology for Clinical and Technological Innovation (SynCTI) and Synthetic Biology Translational Research Programme (TRP) at NUS Medicine.

The team focused on improving **SsdAtox**, a compact DNA editing enzyme that is two-thirds the size of standard base editors but inefficient and prone to side effects in its natural form. Using **AlphaFold3**, an AI-driven protein modeling tool, they identified and modified a key part of the **enzyme (K31)** to widen its DNA entry site, enhancing efficiency. Team also created a novel screening platform, **Trinity-Screen**, to test enzyme variants for efficient DNA editing, minimized DNA breaks, and low cellular toxicity in bacterial cells.

Only the best-performing variants were combined and tested in human cells across 24 artificial and 10 natural gene targets. The **optimized SsdAtox** variants showed up to 11.8 times higher editing efficiency, halved unwanted DNA breaks compared to earlier mutants, reduced toxicity tenfold in bacterial cells, and achieved a 31-fold overall improvement using a new Base Editor Performance Index (BEPI), which balances editing efficiency and damage reduction.

One variant reduced unwanted DNA breaks by 37% compared to BE4max at multiple gene targets and provided a more predictable "editing window." These smaller, improved enzymes are better suited for viral delivery systems, potentially expanding treatment options for genetic diseases. The study also marks one of the first uses of AlphaFold3 to directly

enhance a genome-editing enzyme, offering a framework for developing safer and more precise gene-editing tools.