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MODERN TECHNOLOGY OF BASE EDITING

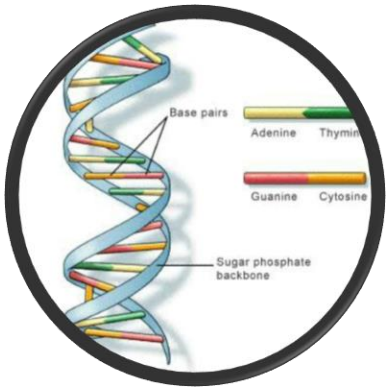
R.NINO FLAVIANA
B. Tech Biotechnology
ninoflaviana@gmail.com

K.KARISHMA
B. Tech Biomedical
karishma3710@gmail.com

ABSTRACT

With the arrival of new classes of single nucleotide editors, researchers can target the most common type of pathogenic **SPN** in humans. The recent genome editing called Base editing a new technique used to swap one DNA genome base pair for another. But current classes of base editors only allow the conversion of cytosine-guanine (C-G) base pair to thymine-adenine (T-A) base pair, rendering a substantial proportion of such mutation untraceable with this approach.

There is no known DNA-targeting enzyme that makes the switch from ADENINE to GUANINE.



ADVANCED GENOME EDITING:

Non-cutting version of the **endonuclease Cas9** which is the current editor of a base –converting enzyme. After base conversion on one DNA strand ,this Cas9 protein makes a mark called a "nick" on the opposite, unedited strand ,prompting the cell's DNA repair mechanisms to replace the original, now mismatched nucleotide and thus complete the base-pair swap.

The cytidine deaminase which only converts the DNA's cytosine to uracil that is equivalent of a thymine base. It's the fact that nature does not provide an enzyme that deaminates adenine in DNA.

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HOW TO BUILD AN ADENINE EDITOR?

An adenine deaminase enzyme in Escherichia coli called **TadA**, which converts adenine to inosine (I) a base that is functionally equivalent to G in transfer RNA (tRNA). Liu and Harvard research associate Nicole Gaudelli decided to create their own DNA editing version of TadA through a combination of direct evolution and protein engineering in E.coli .

They've managed to get something that actually works incredibly well.

First the researchers supplied bacterial genomes with a custom-made, defective version of an **antibiotic resistance gene**. In order to restore **antibiotic resistance activity** they installed mutations that required adenine deamination in DNA which was explained by Liu. These bacteria would die when treated with the antibiotic chloramphenicol-unless they could somehow convert A to I . To examine this A to I conversion ability, the team then created a library of TadA-Cas9 fusions containing various mutations in the adenine deaminase portion of the machinery. Liu said, "They epuipped each of these E.coli cells with the different mutant form of **TadA"**. Nicole made millions of variants in every generation of these TadA mutants, and then required that the bacteria survive in the **presence of growing concentration of antibiotic**.

It was reasoned that the bacteria that made it through this ordeal-that is, those that had fixed their faulty antibiotic resistant genes-must have been harboring TadA mutants that could act on DNA. Only around 3% of sequenced cells showed the change when A-T swapped to G-C in DNA by a particular TadA-Cas9 mutants from a surviving bacteria in human cells. This bacterial system is subsequently investigated to further improve the efficiency of ABE and ensure that bases could be edited in various contexts- for example whether preceded by an A,T,C or G. After several rounds ABE that could convert A into I with minimal errors, at an efficiency of more than 50% -a figure typical of current C-G to T-A base editors.

BASE EDITING – Therapeutic possibilities:

To demonstrate the editor's therapeutic potential, a point mutation associated with a potentially **life threatening iron absorption disorder** called **hereditary hemochromatosis.** The researchers found that, the offending a neucleotide was replaced with the low efficiency of about 30% in human cell line, with no detectable indels.

"THE BASE EDITORS MOVE US CLOSER TO THIS GOAL"

POSSIBILITY OF RNA EDITING WITH "CRISPR-Cas13":

It's still not possible to convert a G to a C, or an A to a T. For example Liu's group is working on developing new classes of base editors to make these changes.

There's a room for improvement with current ABE, too. Bssett notes that the system's editing window –around six nucleotides wide-is large enough that A bases close to the target A may be edited inadvertently. Plus, currently, some DNA sequences are easier to target than others. The researches were working on developing new forms of ABE that maximize their targeting scope and their usefulness. And there were of course using their editors, in collaboration with disease Biology experts, to try to correct animal models of **Human Genetic Diseases.**

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