PRESS RELEASE
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CRISPR-Cas9 Knock-In Efficiency Enhanced Using Small-Molecule Inhibitor Pair, Study Shows

Promega scientists contribute to new research to improve precision and efficiency of groundbreaking gene editing technique

Madison, WI USA. (August 21, 2023) A new study published in *Nature Communications* demonstrates how small molecule inhibitors can be used to improve the precision and efficiency of CRISPR-Cas9 gene editing. The results demonstrate how this groundbreaking technique can be enhanced by using two inhibitors to boost insertion rates and reduce off-target effects. Their findings are key to advancing the use of CRISPR techniques in research and clinical applications using a wide range of cell lines.

Improved Genome Editing with CRISPR-Cas9

CRISPR-Cas9 is a genome editing technique that has become an indispensable tool in biomedical research since it was first unveiled in 2012. Researchers can use the technique to cut DNA at specific sites and insert or remove genetic material, enabling a level of genetic manipulation that was previously impossible.

In the *Nature Communications* paper, the authors analyzed a library of 20,548 small molecules to develop strategies for improving this gene editing technique. They identified two inhibitors targeting the proteins DNA-dependent Protein Kinase (DNA-PK) and DNA Polymerase Theta (PolΘ) and demonstrated that the combination of these two molecules dramatically increased the performance of “knock-in” gene editing. This strategy, dubbed 2iHDR, outperformed previously described strategies that aimed to increase knock-in efficiency with small molecule inhibitors.

This paper also documents a new system based on next-generation sequencing (NGS) that can be used to characterize the effects of inhibitors on CRISPR-Cas9. This open-access tool, which the authors named KI-Seq, enables researchers to analyze the contributions of different DNA repair pathways

following CRISPR-Cas9 treatment. Unlike comparable tools, KI-Seq can be used with any cell type, including non-dividing primary cells.

Promega research scientists Marie Schwinn and Michael Slater contributed to this research led by scientists from AstraZeneca.

Read the paper, "Simultaneous inhibition of DNA-PK and PolΘ improves integration efficiency and precision of genome editing"

Learn about Promega technologies that can be used with CRISPR-Cas9 at www.promega.com/CRISPR

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