**Docket #:** S22-103

# Enhancing Gene Targeting Efficiency in Human Cells with AZD7648 Treatment

Stanford researchers have developed AZD7648, a novel DNA-PK inhibitor that enhances HDR efficiency in CRISPR-Cas9 gene editing by shifting DNA repair from the error-prone NHEJ pathway to the precise HDR pathway, significantly improving gene targeting outcomes in human cells for effective ex vivo gene therapies.

Ex vivo gene therapy is a powerful approach, which involves genetically modifying human cells outside the body using CRISPR-Cas9 technology and then reintroducing them into the patient for treatment of genetic disorders and cancers. Genetic modifications using CRISPR-Cas9 occurs by creating double-stranded breaks (DSBs) in DNA, repaired by either non-homologous end joining (NHEJ) or homology-directed repair (HDR). HDR is more precise but less consistent across different genomic loci due to the inconsistency in the levels of HDR activity, often leading to repairs by error-prone NHEJ pathway resulting in suboptimal therapeutic outcomes. Though DNA-PK inhibitors have been used to improve HDR efficiency, results are inconsistent across different human cell types. There is an urgent need for innovative solutions that enhance HDR efficiency in different genomic loci and cell types.

To address this need, Stanford researchers have developed AZD7648, a novel potent DNA-PK inhibitor to enhance the HDR efficiency in CRISPR-Cas9 based gene editing across different genomic loci. By inhibiting the DNA-dependent protein kinase (DNA-PK), a key component of NHEJ repair pathway, AZD7648 shifts the DNA repair mechanism towards the HDR pathway, allowing for more precise gene modifications. Stanford researchers have demonstrated that AZD7648 treatment outperforms other DNA-PK inhibitors, achieving up to 100% targeting frequency for small nucleotide changes and 80% for large sequence integrations in multiple human

primary cell types. This invention enhances HDR gene targeting efficiency and poised to significantly improve the efficacy of ex vivo gene therapies for treating various genetic diseases and cancers.

**Stage of Development:**
Research - in vitro. The next steps involve in vivo validation of the gene-edited human cells generated with the AZD7648 treatment. Future studies include safety studies using multiple cell types and genomic loci to assess commercial viability.

## Applications

- Ex vivo gene therapy products
- Treatment for various genetic diseases and cancers

## Advantages

- Enhanced HDR-based gene targeting efficiency, applicable in multiple human cell types
- Superior potency and specificity compared to other DNA-PK inhibitors
- Precision and higher gene targeting frequencies, when compared to current methods
- Therapeutic relevance with ongoing clinical trials for solid tumors

## Publications


- Selvaraj S, Feist WN, Viel S, Vaidyanathan S, Dudek AM, Gastou M, Rockwood SJ, Ekman FK, Oseghale AR, Xu L, Pavel-Dinu M, Luna SE, Cromer MK, Sayana R, Gomez-Ospina N, Porteus MH. High-efficiency transgene integration by homology-directed repair in human primary cells using DNA-PKcs inhibition. Nat Biotechnol. 2024 May;42(5):731-744.


## Patents

- Published Application: WO2023220418
- Published Application: 20250305004

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