

Pin-point™ – A Modular Base Editing System Driving Cell and Gene therapies

Horizon's modularly designed Pin-point base editing system uses a nickase Cas9 with an aptameric guide RNA (gRNA) to recruit a deaminase to a DNA locus of interest. We optimized design and delivery conditions of chemically synthesised gRNAs and *in-vitro* transcribed mRNAs to apply multiplex base editing to the development of engineered CAR-T cells. We demonstrate simultaneous targeting of several therapeutically relevant loci with high efficiency and precision, while retaining proliferative and cytotoxic ability. Compared to Cas9-mediated knockout, Pin-point base editing enables higher cell viability, less gRNA-dependent off-target editing and reduced frequency of chromosomal translocations. An additional advantage of Pin-point base editing technology is the aptameric recruitment of deaminases, which enables robust simultaneous knock-in and knockout in the same cell and the ability to easily customise the most effective deaminase for each target. The efficient and precise edit of multiple cell types, including human induced pluripotent stem cells, allows for a variety of therapeutic applications and a potential to treat both monogenic and polygenic disorders, opening the door to more sophisticated cell and gene therapies.