NIHR Great Ormond Street Biomedical Research Centre

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Gene Editing in X-Linked Agammaglobulinaemia

This project is a pre-clinical feasibility study to design a gene editing strategy for X-Linked Agammaglobulinemia (XLA). This is caused by a mutation in the Btk gene which leads to an absence of B Cells and an absolute antibody deficiency. The resulting severe and frequent infections lead to recurrent hospital admissions and significant morbidity.

Rather than try to repair an individual mutation we insert a functional version of the minigene in the correct location in the genome. Hence, creating a universal treatment strategy. Firstly, Cas9 protein complexed with guide RNA causes a double stranded break in the Btk gene. Subsequently an Adeno Associated Virus (AAV) delivers the gene into the area of the break.

We initially showed integration and restored Btk expression using our technique in a Btk knockout B cell line. We then edited stem cells from 3 XLA patients and demonstrated restored development of immature B cells.

We now aim to perform further functional studies to assess if these edited stem cells express the Btk protein and can differentiate into non-lymphoid lineages. Finally, we will test their ability to become activated and produce Immunoglobulins. These assays are precursors to scale up studies and Phase 1 trials.