Biomere

COMMUNITY BLOG

CRISPR BASED THERAPIES - FROM PLATE TO PATIENT

CRISPR technology is one of the most powerful tools in disease research with the potential to correct genetic defects that cause diseases. CRISPR-mediated gene correcting can either be used to develop curative therapies or prevent onset of disease by correcting the gene defect very early. CRISPR was first described in 2012 and the landmark publication that described the complete CRISPR-Cas9 system was published in the journal *Science*[1]. Since the first report, the number of publications has been steadily increasing – over 17,000 papers on CRISPR were published in 2018[2] and the numbers continue to increase. This is clear evidence that CRISPR is being widely adopted in research and development applications. Another breakthrough in CRISPR technology was the launch of the first clinical trials. Several early-stage clinical trials have been launched and completed in various disease areas including cancer, blood diseases, and rare diseases[3].

The first cancer clinical trial using CRISPR was performed in China in 2016 where non-small cell lung cancer patients was injected with PD-1 edited T cells in a phase I trial to evaluate the safety of the therapy. The results from this study were published in 2020[4], and overall, the edited T-cells were well tolerated and the off-target effects of CRISPR gene editing were infrequently found. The first clinical trial in the US used a more complicated approach where CRISPR was used to knockout PD-1 and endogenous T-cell receptor and introduce an engineered T-cell receptor in T-cells. These engineered T-cells were introduced into 3 patients – 2 with advanced refractory myeloma and one with metastatic sarcoma). The study found that the multiplex CRISPR-edited T-cells showed an acceptable safety profile and the engineered T-cells were detectable in the patients' bone marrow and tumors[5].

Correcting underlying issues in blood diseases has been an active area of CRISPR research. The first report of CRISPR-based therapies was a study done in 2019 on beta-thalassemia patients where edited hematopoietic stem cells from healthy donors were successfully introduced into patients. The first patient with sickle cell disease, Victoria Gray, was also treated in 2019 with edited cells and the results have shown that this approach is successful in increasing hemoglobin levels to close to normal and more importantly, the engineered cells are detectable in the bone marrow suggesting that infusion of CRISPR-edited cells could have a long-term effect in patients with sickle cell disease or beta-thalassemia[3]. More recently, scientists at UCSF, UC Berkeley and UCLA have launched an early-stage trial to test a CRISPR solution to directly correct the sickle cell mutation in the patient's own blood cells[6] that has the potential to be a true cure.

The first trial in an eye disease was launched last year where patients with Leber congenital amaurosis 10 (LCA10) were dosed with an adeno-associated virus (AAV) carrying the Cas9 protein and guide RNA under the control of a tissue-specific promoter so that the CRISPR system is only expressed in photoreceptor cells[7]. LCA is caused by mutations in the centrosomal protein 290 so correction of the genetic defect in the gene is hypothesized to improve vision in LCA patients. Injecting the CRISPR system directly into the eye has significant advantages since the eye is immune-privileged and contained so there is a lower risk of off-target effects outside the eye. Indeed, in mouse studies, about 10% of photoreceptor cells showed the edit and this level of correction is considered to be sufficient to improve vision.

Based on these recent trials, it is clear that CRISPR is progressing beyond a powerful research tool and developing into a truly curative system for several diseases. Monitoring the off-target effects and adverse events in patients are critical to understand the short and long-term implications of CRISPR therapies and ensure that the system is used in an ethical way to improve patient lives and cure diseases.

References:

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