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How CRISPR-CAR-T therapy uses patient's immune system to fight cancer

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Gene-editing pioneer Jennifer Doudna's discovery on Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR Associated Nuclease 9 (CRISPR/Cas9) technology has brought about several new avenues in cancer treatment. This tool uses only a single nuclease protein complex with 2 short RNA as a site-specific endonuclease, which makes it a simple, powerful, and flexible genome editing tool to target nearly any genomic locus. Also, recent developments in therapeutic engineered T cells and effective responses of CD19-directed chimeric antigen receptor T cells (CAR-T) therapy has been rapidly growing in cancer therapy. The combination of CRISPR/Cas9 technology as a genome engineering tool and CAR-T cell therapy (engineered T cells that express chimeric antigen receptors) is leading to further explorations in cancer treatment.

For years now, cancer patients have been treated with various types of therapies, including conventional strategies like chemo-, radio- and targeted therapy, as well as immunotherapy like checkpoint inhibitors, vaccine, and cell therapy, etc. Among the therapeutic alternatives, T-cell therapy like CAR-T (Chimeric Antigen Receptor Engineered T cell) and TCR-T (T Cell Receptor Engineered T cell), have emerged as the most promising therapeutics due to its precision clinical efficacy.

According to Research&Markets, in 2012, there were only 12 clinical trials investing in CAR-T cell therapy products. Today, that number has risen to over 500. Between 2017 and 2021, four CAR-T products have hit the market and this number is projected to reach double digits within five years. The earliest approvals, Kymriah and Yescarta, have been commercially available since 2017 and 2018, respectively, and have been infused into nearly a half million patients worldwide. In July 2020, the US Food and Drug Administration (FDA) approved a third CAR-T cell therapy, Kite Pharma's brexucabtagene autoleucel (sold as Tecartus). In February 2021, Breyanzi became the fourth CAR-T approved cancer therapy.

More recently, the antitumour activities of CAR-T cells have shown great improvement with the utilisation of CRISPR/Cas9 gene editing technology. It has been found that the genome editing system could be a powerful genetic tool to use for manipulating T cells and enhancing the efficacy of cell immunotherapy. Before CRISPR was invented, CAR-T cells were generated using other genome engineering technologies. As CRISPR/Cas9 gene editing enables manufacturing of CAR-T cells with improved anti-cancer effects, considering the heterogeneity of cancer cells, this therapeutic approach is believed to have improved treatment outcome where the immunotherapy not only treats the cancer condition but also enhances the

normal capacity of the patient's immune system.

Dr Shailendra Vyas, a scientist turned-entrepreneur and Founder of Bioheaven360 Genotec Pvt Ltd, opines that CRISPR has been identified as the next generation technology for cancer cell editing and treatment. He says, “The biggest advantage can accrue from the fact that there are so many genes which can cause cancer and the mutations differ between patients. Thus, what we see is as many CRISPR clinics upcoming wherein gene editing can be done and directed therapies can be given to patients. The biggest advantage is that the therapies can be of low cost and effective.”

Also, conventional cancer treatments, like radiation therapy or chemotherapy, cannot discriminate between healthy cells and cancerous cells. This means that the treatment destroys both types of cells, resulting in severe side effects. In contrast, CAR-T therapy uses a patient’s own immune system to fight cancer. Explaining from his company’s research standpoint, Dr Vyas says, “Bioheaven360 is trying to understand the downstream and off-target effects of CRISPR edited cells. We focus mainly on the regulators that are a part of natural defence mechanisms in cells and may act as a hurdle to CRISPR applications. Gene editing will take its own time till it reaches the market as cancer therapy. In India, where a large part of the population requires low-cost treatments 'asap!' We must not ignore other established immediately possible solutions like recombinant therapeutic antibodies or CAR T-Cell therapies or look towards other cost-effective solutions. CRISPR based CAR T-cell therapies are gaining popularity and will be of significance in the near future.”

Scientists, therefore, are confident that exploring both gene-edited cell treatments will empower the treatment of numerous sorts of cancer. The surface is being scratched and this combination tool will open up several new avenues to cost-effective cancer treatments and become the go-to treatment mode in the personalised cancer medicine arsenal.

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