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Science as a Human Endeavour: CAR-T Cell Therapy

Background:

With approximately 9.8 million people dying each year from cancer, scientists and practitioners worldwide are responding by seeking new cancer treatments. Immunotherapies are prospective cancer treatments that modify a patient's antibodies to target cancer cells. Chimeric Antigen Receptor (CAR) T-Cell Therapy is a recent form of immunotherapy that has shown promising results in clinical trials for cancers like leukemia and lymphoma[1]. Areas of biotechnology and nanotechnology have **influenced** the development and improvement of CAR-T cell therapy as an effective immunotherapy. Despite the promising **application** of CAR-T cell therapy for patients with haematological malignancies, the **limitations** of its side effects and social concerns raises questions of its role in society.

Relevant Biology Concepts:

Cancer is caused by abnormal cell division that results in the deterioration of body tissues. The body's adaptive immune system fights cancerous tumours through the action of T-cells, which detect the Major Histocompatibility Complex (MHC) on cancerous cells and deactivate them by binding with surface receptors[5]. However, cancerous cells can downgrade or mutate the MHC complex, inhibiting the T-cell's ability to identify and elicit a response against them.

CAR-T cell therapy is a form of adaptive cell transfer (ACT) which involves modifying patient T-cells via genetic engineering[4]. T-cells in the patients' blood are extracted by leukapheresis, where blood components are selectively filtered from the body[4]. Genetically engineered viral vectors inject a desired gene into the T-cell's DNA[4]. Changing the genetic sequence in T-cells enables them to produce Chimeric Antigen Receptor (CAR) proteins which target tumour receptors. Therefore, CAR-T cells deactivate tumours without MHC restrictions, as CAR's are specifically structured to be complimentary with tumour receptors[5]. CAR-T cells are then cultured and multiplied, increasing the potency of immune response received by patients. These mature CAR-T cells are administered in patients and their side effects are monitored (Figure 1). Specialists may then use nanoparticle drug carriers to improve potency of response and deliver the desired gene to the T-cells.

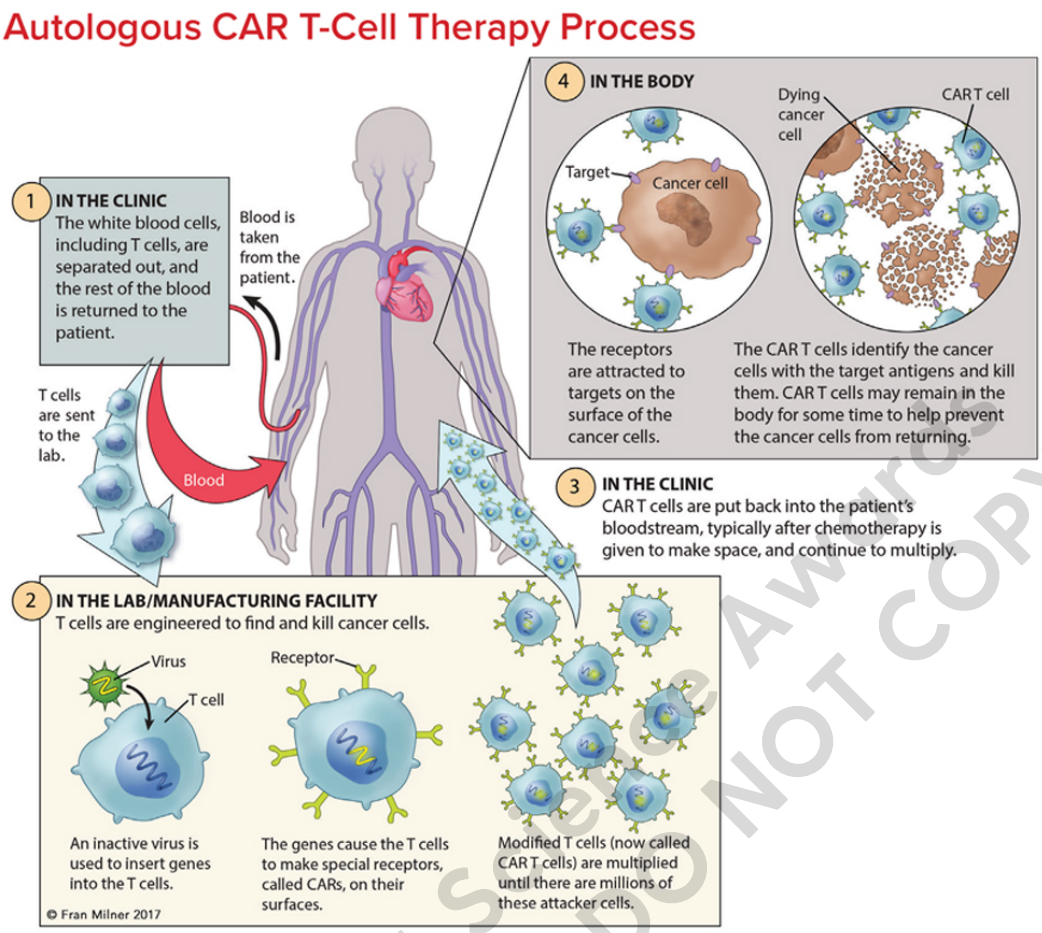

Figure 1: Stages of CAR-T Cell Cancer Therapy

Influence:

Advancements of nanotechnology have greatly influenced the model of CAR-T cell therapy in society. Conventional CAR-T cell therapy has limited response to solid tumours, as their microenvironment causes a formidable barrier to suppress T-cells[7]. Nanoparticles are synthetic carriers which are injected in the bloodstream and deliver a desired gene to the T-cells to then produce receptor proteins for tumour cells (Figure 2). Current application of liposome-based nanoparticles has influenced CAR-T cell therapy by improving delivery of desired gene whilst evading the tumour's microenvironment[6]. The Fred Hutchinson Cancer Research Institute designed nanoparticles which infuse receptors on CAR-T cells that bind with CD-19 receptor on tumour cells. Trials with Acute Lymphoblastic Lymphoma mice showed that 90% of mice with nanoparticles went into remission and had significantly decreased tumour count[7]. Results showed that nanoparticles blocked suppressor cells in the tumour microenvironment whilst simultaneously stimulating key anti-tumour components of the CAR-T cell[7]. Scientists believe programming nanoparticles to deliver multiple CAR's may improve the response of tumour cells via multiple angles[1]. Ultimately, a greater

understanding of nanotechnology and its application can influence the successful execution of CAR-T cell immunotherapy.

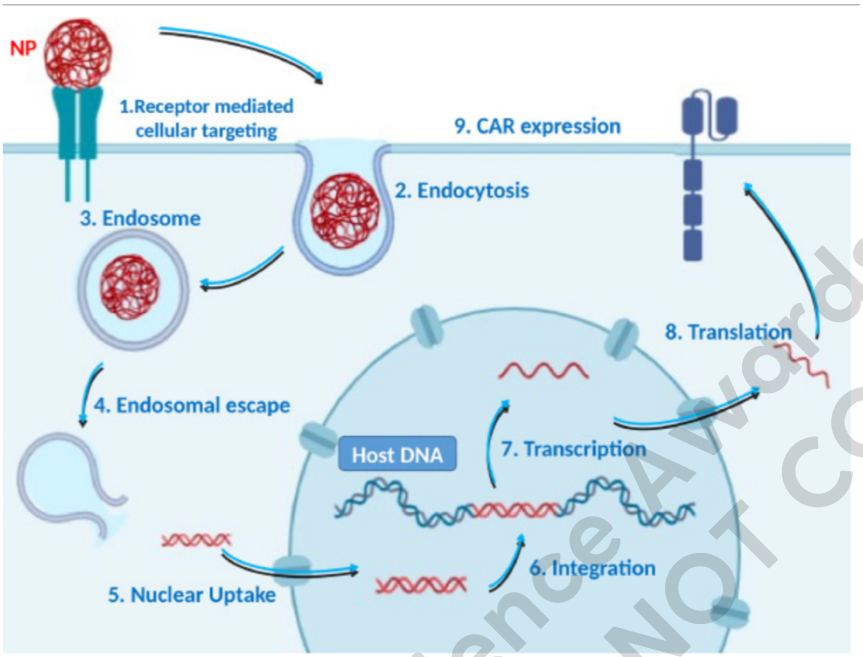

Figure 2: Process of using Nanoparticle in CAR-T cell Therapy

Gene-editing technologies such as CRISPR/Cas-9 have influenced CAR-T cell functionality. The body's immune response is regulated by Programmed Cell Death Protein-1 (PD-1 pathway), which suppresses the activity of T-cells and down-regulates the immune system[6]. CRISPR/Cas 9 technology can disrupt the inhibitory effects of PD-1 pathway by silencing the PD-1 gene. In 2019, preclinical trials utilised adenine-base CRISPR technology to alter the PD-1 gene, where decreased expression of the PD-1 protein subsequently prolonged T-cell activity[6]. The American Association of Cancer Research found that reducing expression of PD-1 gene in anti-prostate stem CAR-T cells significantly improved their efficacy against tumours[4]. Researchers extended CRISPR's influence to silence genes which disrupt inhibitory receptors or potentially produce universal allogenic CAR-T cells for treatments[1]. The exploration of epigenetic modification methods has demonstrated the influence of technology in improving the efficacy of CAR-T cell therapy.

Application and Limitation:

The application of CAR-T cell therapy has shown promises in treatment of patients with Acute Lymphoblastic Leukemia (ALL). ALL affects bone marrow through the overproduction of white blood cells[8]. Patients with ALL have limited treatment options, as tumour cells are prone to reappear after treatment. Therefore, CAR-T cell therapy enables the body to gain an immunity and utilise modified T-cells to fight ALL. Axicabtagene Ciloleucel is a CAR-T cell therapy trialled for ALL patients with non-Hodgkin Lymphoma and showed recovery rates of 70%, where its unique cell structure reduced adverse side effects from treatment[8]. Larger clinical trials lead to the FDA approval of Tisagenlecleucel, showing 80% remission rate for ALL patients[8]. Marta Coscia of Frontiers in Oncology commented that *"unprecedented CR rates achieved in almost all trials imparted the credibility to CAR-T cell therapy"*[2]. CAR-T cell therapy has advantages comparing with other treatments, due to its unique specificity for tumour cells and therefore decreased likelihood in damaging body tissues. The flexibility of intracellular signals by the T-cells, enables them to evade defence mechanisms employed by tumour cells[6]. Evaluation of current understanding in CAR-T cell therapy reveals the desirable prospect of utilising this immunotherapy, where further studies should be conducted to confirm its general approval for ALL. Therefore, current application of T-cells in ALL indicates the prospective nature of it becoming a standard intervention.

However, the presence of adverse side effects has limited the approval of CAR-T cell therapy. T-cells elicits an immune response through the release of cytokines, messenger molecules which signal the T-cells to perform its function in eradicating the tumour. The expansion of CAR-T cells can lead to Cytokine Release Storm (CRS), where large amounts of cytokines are released into the bloodstream and cause severe organ dysfunction[1]. Researchers believe that the CAR's structure and antibody affinity may have correlative toxic side effects[1]. Concerns with CAR-T cells cross-reacting with normal antigens on non-cancerous cells and damaging healthy tissue, imposes potential patient harm[5]. Furthermore, CAR-T cell therapy can cause insertional oncogenesis, where viral vectors are abnormally inserted in the T-cells genome and can become cancerous[5]. Significantly altering the genome has marked ethical concerns due to potential changes in patient's DNA. Concerns of researchers mishandling CAR-T processes, requires strong implementation of policies to regulate this treatment. Understanding of these biological processes are based on insufficient findings, where limitations have halted CAR-T cells therapy's role in society.

Discussion:

Economic considerations of CAR-T cell therapy have raised concerns of ensuring equitable access of these treatments. Individual cost of treatment is usually $373,000, however projected costs for additional associated care when managing side effects can reach $1.5 million (Figure 3)[3]. Kathleem Imbach at 'Gene & Cell Therapy' stated that *"CAR-T cell therapy and associated costs"* from complex manufacturing supply chain may make treatment to be *"unfairly stratified in socioeconomic lines"* due to the disadvantages towards those less financially stable[3]. High-cost treatments and rapid deterioration of a patient's condition may disincentivise individuals in receiving potentially beneficial treatments. Evaluation reveals that greater involvement of government reimbursement scheme and subsidies of these treatments, is required for CAR-T cell therapy to become financially reasonable. Ultimately, the commercialisation of CAR-T cell therapy should consider patient's economic concerns and their ability to receive affordable treatment.

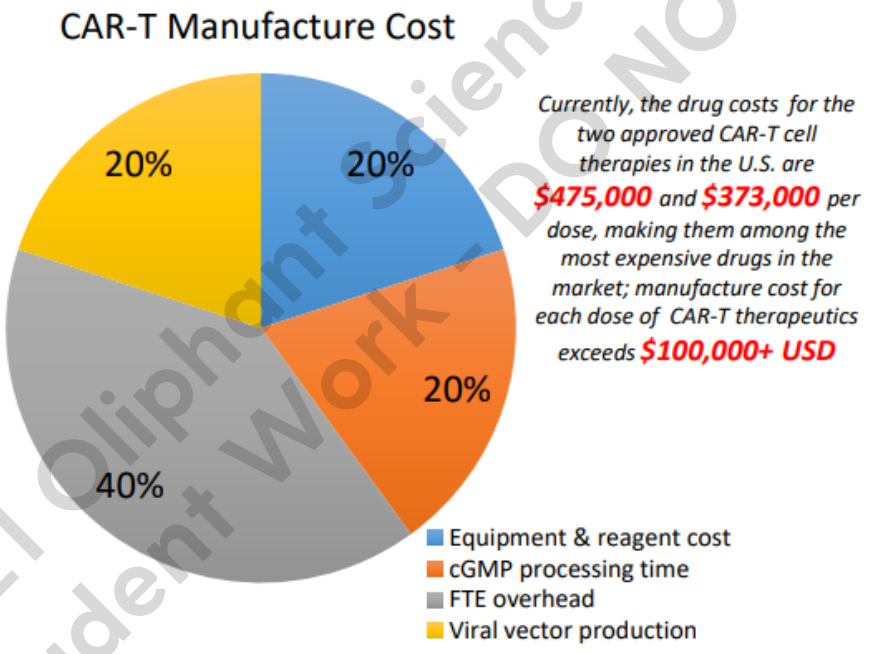

Figure 3: Manufacturing Costs of CAR-T Cells in America

Additionally, the application of CAR-T cell therapy has been influenced by social demand despite the absence of clinical approval. The "compassionate use" policy in the US enables patients with life-threatening illnesses, like cancers, to participate in investigational trials without approval of treatment[3]. Therefore, some patients partake in these trials in the hope of accessing new therapies and may steer away from conventional treatment to their detriment. Firms who incentivise financial gain and deny distribution of treatment may experience public backlash. Therefore, the role of CAR-

T cell therapy is presented with an ethical dilemma, as respecting patient autonomy and minimising patient harm from uncertain side-effects must be equally acknowledged. Ethical concerns may extend to the availability of treatment, where limited manufacturing sites may cause healthcare workers to make tough decisions on who receives treatment[3]. Overall, current understanding of CAR-T cell therapy has meant manufacturing firms must manage public demand whilst also ensuring patient safety.

Deeper examination of CAR-T cell's role in society reveals the importance of manufacturers maintaining ethical standards and adhering to strict FDA requirements when approving the immunotherapy. Researchers at 'Gene & Cell Therapy' believe *"it would be preferable for CAR-T cell therapy to expand slowly",* where scientists should gain a better understanding of its health effects before approving treatment[3]. The inception of regulatory bodies such as Switched Oncology, are examples of government institutions which address benefits and limitations of CAR-T cell therapy so that patients can make informed decisions[4]. Ultimately, individuals in society should wait for conclusive findings in order to ensure optimal treatment in the future.

Conclusion:

Overall, the development of CAR-T cell therapy has provided an alternative solution for patients dealing with the debilitation of cancer. Refining procedures and alternatives to these treatments stem from the influence of various technologies when improving its effect on patients. However, the limitations of its harmful side effects and concerns economically and ethically, imply that greater research and interaction with society is needed before it becomes a standard intervention.

Word Count: 1500

SHE Article:

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