SASTA OLIPHANT SCIENCE AWARDS

SOUTH AUSTRALIAN SCIENCE TEACHERS ASSOCIATION

Prize Winner

Science Writing

Year 11-12

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INTRODUCTION

Chimeric antigen receptor (CAR) T-lymphocyte therapy refers to genetically engineering T-lymphocytes to express synthetic receptors that specifically terminate cancerous cells, resulting in higher levels of efficacy then less targeted existing treatments such as chemotherapy (Mueller, 2017) (National Cancer Institute, 2022). They are used to treat haematological malignancies – blood cancers including leukemia, lymphoma and multiple myeloma that debilitate over 110,000 Australians (Australian Institute of Health and Welfare, 2021). However, despite the medical benefits associated with this immunotherapy's **application**, **limitations** in the form of unexpected health consequences along with intertwined economic, social, and ethical considerations **influence** its widespread clinical implementation (Borgert, 2021).

BIOLOGICAL CONCEPTS

Proto-oncogenes, which code for proteins that regulate normal cellular division, become oncogenes when mutated (Brown, 2021). Cancer is uncontrolled cellular growth from increased epigenetic expression of oncogenes and epigenetic downregulation of tumour suppressor genes, or mutations that compromise the structure and consequent function of tumour-suppressor proteins (Baylin & Jones, 2016). The abnormal proteins synthesised from oncogenic mutations are termed tumour-specific antigens (Vigneron, 2015). Proteins synthesised in normal cells but up to 100x more in cancerous cells due to non-oncogenic mutations are called tumour-associated antigens (Mak & Saunders, 2008).

T-lymphocytes, immune cells essential for exterminating cancerous cells, possess numerous membrane-bound T-lymphocyte receptor (TCR) proteins (Hochstenbach, 1992). Demonstrated below in **Figure 1**, to initiate an immune response, the TCRs' binding site complementarily binds to specific cancerous antigens, but **only** those bound to a protein group named the major histocompatibility complex (MHC) (Hennecke & Wiley, 2001).

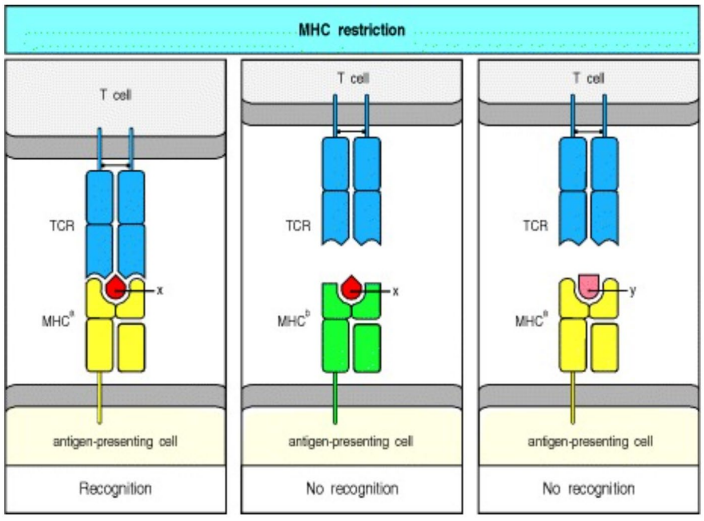

Figure 1: TCR's specificity to an MHC-antigen complex (Janeway Jr, et al., 2001).

Therefore, in order to evade TCRs, cancerous cells develop the ability to prevent the transcription of MHC genes through epigenetic mechanisms including DNA hypermethylation (Suárez-Álvarez, et al., 2010). This reduces the formation of MHC-antigen complexes, preventing TCR binding and allowing cancerous cells to proliferate (Beatty & Gladney, 2016).

However, not all cancerous antigens are MHC-bound and, thus, this resistance can be overcome through genetically modifying T-lymphocytes to express CARs that bind to MHC-independent antigens (Chmielewski, et al., 2013). In this process, firstly leukapheresis is performed, a procedure involving patient blood collection and the subsequent isolation of T-lymphocytes (Smith, 1997). The isolated T-lymphocytes can then be genetically engineered to express a CAR, shown in **Figure 2** below.

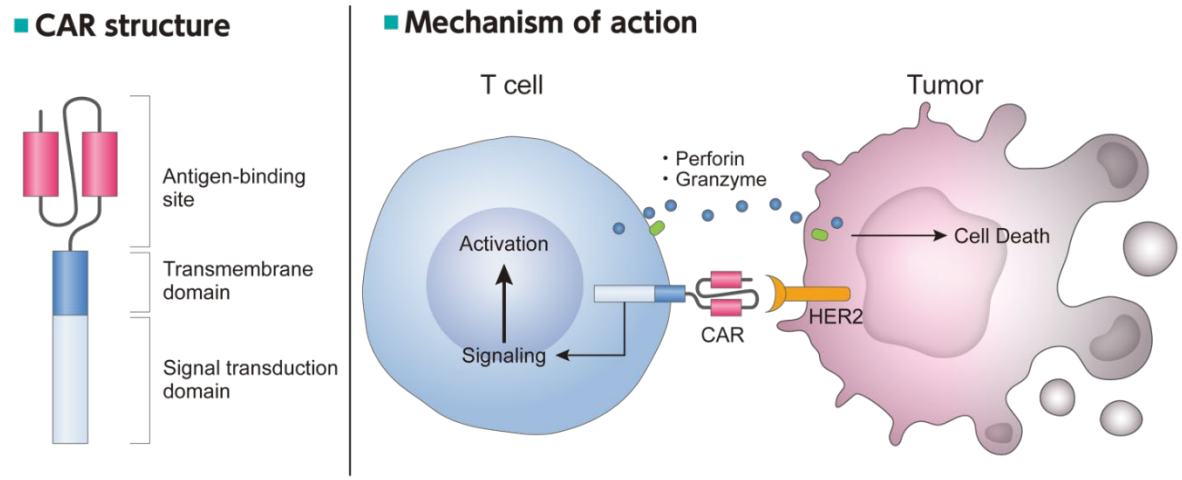

Figure 2: CAR structure and antigen-binding (Shinshu University, 2019).

Most importantly, unlike TCRs, the peptide sequence of the CAR's antigen binding site is designed to be complementary to a specific **independent antigen** rather than an MHC-bound antigen, overcoming the attempts of cancerous cells to resist immunorecognition through MHC downregulation. When the CAR binds to an antigen, the intracellular signalling domain signals to the CAR T-lymphocyte to activate an immune response, releasing inflammatory cytokines and toxins such as perforin and granzyme, as shown in **Figure 2** (Benmebarek, et al., 2019).

The CAR's genetic sequences are transduced into the isolated normal T-lymphocytes, typically using a viral vector, allowing the T-lymphocytes to express these CARs on their membrane. Finally, the genetically engineered CAR T-lymphocytes are cultured, replicated and intravenously infused into the patient (National Cancer Institute, 2022). Located in the blood, these CAR T-lymphocytes primarily target haematological malignancies rather than solid tumours, as traversal into the latter presents a physical challenge (Sterner & Sterner, 2021).

APPLICATION AND LIMITATION

Clinical experiments involving patients with different forms of haematological malignancies have demonstrated that CAR T-lymphocyte therapy is significantly more effective than chemotherapy, the current standard treatment for blood cancers (National Institute for Health and Care Excellence, 2016). A medical study revealed that 90.9% of acute lymphoblastic leukemia patients treated with CAR T-lymphocyte therapy achieved remission within four weeks, substantially higher than the 37.9% remission rate of those treated with chemotherapy (Wei, et al., 2018).

Furthermore, as demonstrated below in **Figure 3,** CAR T-lymphocyte therapy provides far more sustained action than chemotherapy (Jain, et al., 2018).

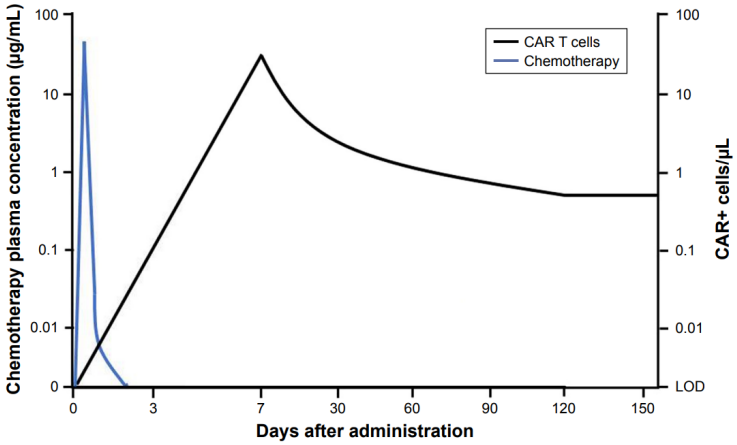

Figure 3: Comparison of CAR T-lymphocyte and chemotherapy drug serum concentration 150 days from administration (Jain, et al., 2018).

Correspondingly, in a study investigating the overall survival rate (proportion of patients still alive after treatment) of diffuse large B-cell lymphoma patients, patients treated primarily with chemotherapy had a one-year overall survival rate of 28% (Crump, et al., 2017). Four studies involving CAR T-lymphocyte therapy for the same condition reported roughly doubled one-year overall survival rates, ranging between 48-59% (Ernst, et al., 2021).

Consequently, due to chemotherapy's impermanence, patients typically require 4-6 cycles of treatment and recovery, with each cycle often lasting weeks, accumulating into several months (Weaver, 2021). Comparatively, CAR T-lymphocyte therapy involves only one administration and has a considerably shorter treatment time-frame, allowing for faster treatment and, therefore, benefitting more patients (Reshef & van Besien, 2019). After infusion, patients typically remain hospitalised for care and monitoring, with a study involving non-Hodgkin lymphoma patients treated using CAR T-lymphocyte therapy observing a median of 16 hospital days in the absence of complications (Kilgore, et al., 2019). When factoring up to 3 weeks for leukapheresis, genetic engineering and shipping (Cancer Treatment Centers of America, 2018), this approximates to about 5 weeks.

However, unexpected health consequences limit the treatment's usage, presenting the opportunity for innovation in the form of pharmacological solutions (Pereira, et al., 2021).

Two conditions - cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) - are the primary side-effects of CAR T-lymphocyte therapy (St. Jude Children's Research Hospital, 2019) (Neill, et al., 2020). A study including 84 patients found that, following CAR T-lymphocyte infusion for lymphoma, 80% of patients experienced CRS, whereas ICANS inflicted 40% of patients (Belin, et al., 2020). In addition to sometimes severe symptoms, both diseases can result in fatality, with CRS having a mortality rate of 1.48% and neurotoxic disorders having a rate of 0.91% across 1200 CAR T-lymphocyte therapy patients (Cai, et al., 2020).

As CRS is well-understood to directly result from CAR T-lymphocytes releasing excess cytokines, treatments including tocilizumab which counteract excess cytokine production have been clinically-approved (Le, et al., 2018). No approved pharmacological treatments for ICANS currently exist due to little knowledge regarding its biological mechanisms (Shabir, 2020) (Yáñez, et al., 2020). However, recent scientific inquiry has enabled scientists to identify a correlation between high levels of interleukin-1 cytokines in cerebrospinal fluid and ICANS following CAR T-lymphocyte therapy. Consequently, scientists have initiated trials involving the administration of anakinra, an interleukin-1 inhibitor, as a pharmacological remedy for ICANS. Preliminary trials have demonstrated considerable effectiveness, with one small-scale trial achieving a 55% response rate. However, this novel treatment is currently in early experimental stages, and more scientific experimentation and monitoring is required to evaluate the safety and efficacy of the treatment prior to clinical approval (Wehrli, et al., 2022). Overall, further scientific inquiry is pertinent in increasing understanding regarding the physiological mechanisms that underpin ICANS to facilitate the design of more solutions (Shabir, 2020).

The ubiquity of these complications not only pose serious health-risks to patients, but also consequently limit CAR T-lymphocyte therapy to conservative clinical use, reducing the potential number of patients that could benefit from the treatment (Ledford, 2022).

INFLUENCE

Socially, the necessity of implementing efficient treatments for haematological malignancies such as CAR T-lymphocyte therapy is exemplified through the disease's burden on Australian society.

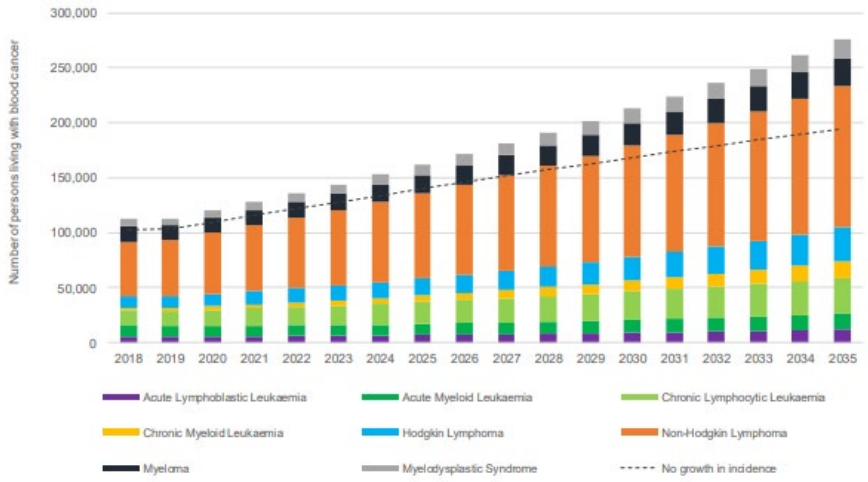

Figure 4: Projected prevalence of haemotological malignancies in Australia from 2018 to 2035 (Insight Economics & Australian Leukemia Foundation, 2019).

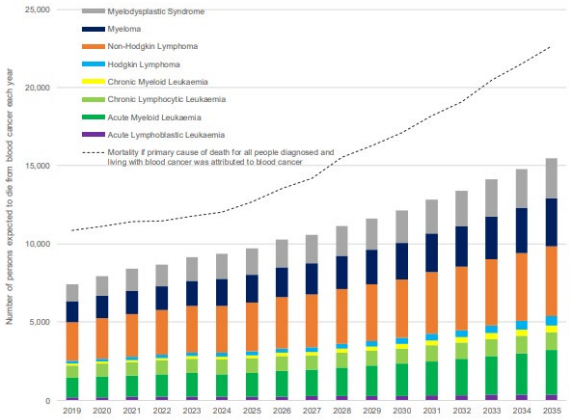

Figure 5: Projected mortality of haematological malignancies in Australia from 2018 to 2035 (Insight Economics & Australian Leukemia Foundation, 2019).

A recent epidemiological report by the Australian Leukemia Foundation indicated that the prevalence and mortality rate of haematological malignancies are both predicted to rise significantly. **Figure 4** and **Figure 5** show that approximately 275,000 Australians are estimated to be living with the disease in 2035, with over 15,000 resultant fatalities (Insight Economics & Australian Leukemia Foundation, 2019).

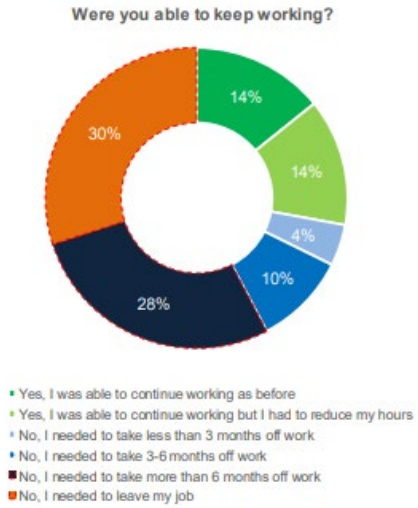

Figure 6: Influence of haematological malignancies on employment of affected patients (Insight Economics & Australian Leukemia Foundation, 2019).

Furthermore, the majority of diagnosed patients require time off work, 30% of whom are forced to forfeit their job entirely as displayed in **Figure 6** (Insight Economics & Australian Leukemia Foundation, 2019). This would have negative implications for not only the individual and their family, but also on the rest of Australian society, as unemployment elevates welfare funding requirements, increasing taxes (Cassidy, et al., 2020).

Despite CAR T-lymphocyte therapy's potential to reduce the detrimental health and economic impacts of haematological malignancies, expenses involved in the therapy present an implementational barrier. The standalone price for the administration of CAR T-lymphocyte therapy ranges from $522,834 AUD to $665,639 AUD. When factoring in complication-related hospitalisations – primarily resulting from CRS and ICANS – which incur a median cost of $564,372 AUD, overall treatment expenditure can exceed well over $1 million AUD (Borgert, 2021). Such prices may prevent socioeconomically disadvantaged patients from accessing potentially life-saving treatment or plunge many individuals into medical debt.

To mitigate the effect that socioeconomic health disparities would have on the accessibility of the treatment, the Australian Federal Government has recently implemented Medicare subsidies to significantly reduce or remit costs for two of three federally-approved CAR T-lymphocyte therapies (Hunt, 2020) (Hunt, 2021). However, due to high prices and facilities only being located in certain locations, subsidiary programs are constrained by stringent selection processes (Novartis, 2021) (Lymphoma Australia, 2021). This raises the ethical dilemma of denying certain individuals potentially life-saving treatment over logistics such as geographical accessibility. Further monitoring, evaluation and potentially economic expansion of these treatment programs and their selection processes are required to address these implementational issues (Velickovic & Rasko, 2022).

CONCLUSION

CAR T-lymphocyte therapy's **application** in cancer therapy offers a highly effective means of treating haematological malignancies. The implementation of this treatment is **influenced** and necessitated by the worsening epidemiological outlook of the disease in Australia, and the consequent pertinence of improving pre-existing, less effective cancer treatments. However, **limitations** in the form of health side-effects compromise its widespread application, as do economic **influences**. Furthermore, although the Australian government has implemented subsidies to offset treatment expenses, strict selection processes due to limited funding and facilities precipitate concerns regarding ethics and social equity. Nevertheless, through using scientific inquiry and knowledge to develop solutions for associated health side-effects while improving treatment programs to ensure economically and socially equitable access, this novel therapy could positively transform the prognosis of patients diagnosed with haematological malignancies in Australia.

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