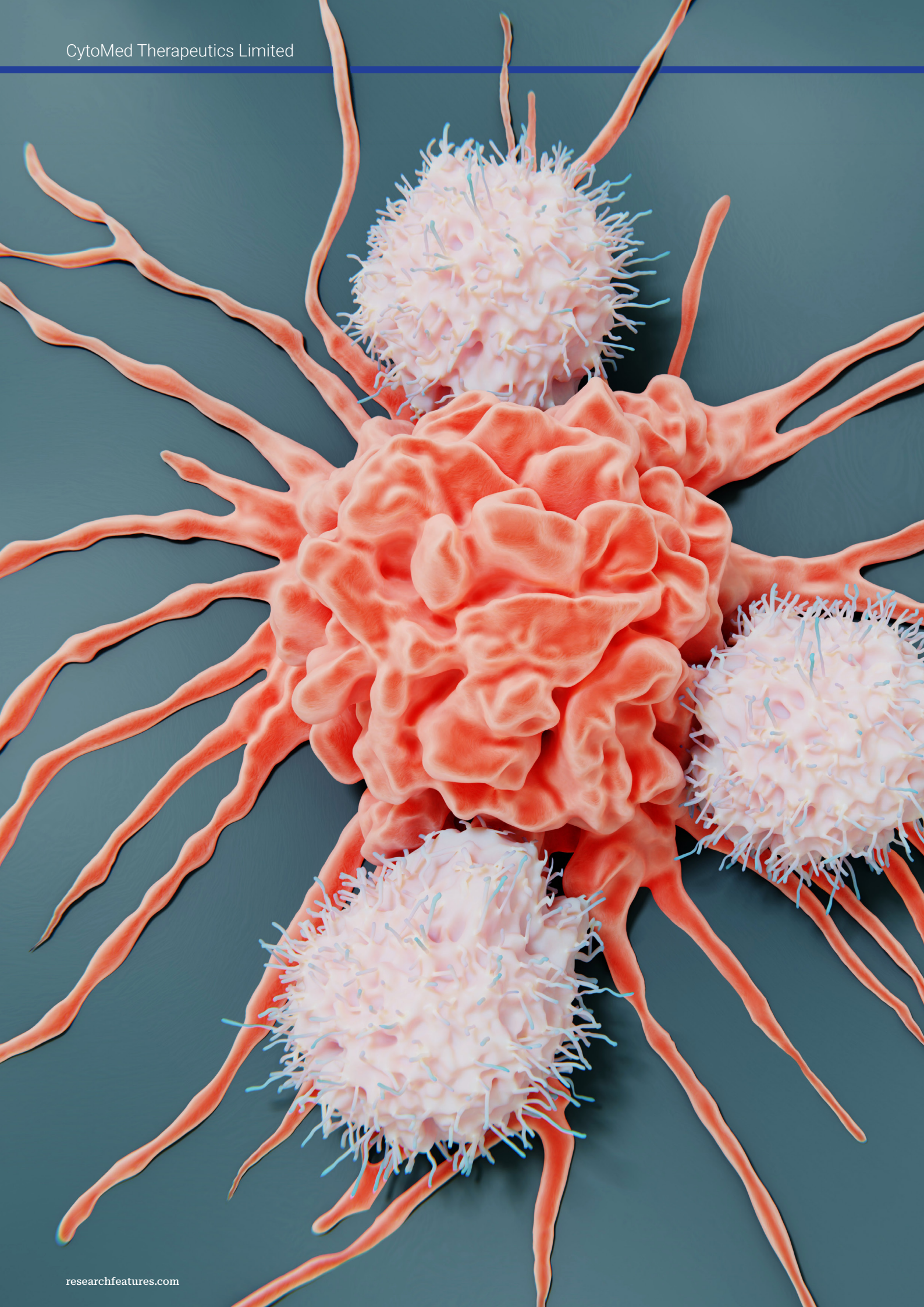


CytoMed

Revolutionising CAR-T therapies

- Adoptive cell therapy (ACT) is a type of immunotherapy that uses modified immune cells to treat cancer.
- Chimeric antigen receptor (CAR)-T cell therapy is a type of ACT that uses CAR-modified T cells to specifically target cancer cells.
- γδ T cells represent a small population of T cells (1–5%) that may recognise cancer cells even without modification.
- Induced pluripotent stem cells (iPSCs) are a type of stem cells that have unlimited self-renewal capability and potential to be transformed into any cell type.
- CytoMed Therapeutics Limited is developing both γδ T cell and iPSC-based cell therapy products for cancer treatment.

Immunotherapy is a form of cancer treatment that uses our immune system to combat cancer. Our immune system is comprised of various types of immune cells, including white blood cells that help us fight infection and cancer. Among the white blood cells, T cells play an essential role in infiltrating tumours, targeting and destroying cancerous cells.

A rapidly evolving area of immunotherapy, adoptive cell therapy (ACT), uses modified immune cells to treat cancer. During ACT, T cells are taken from the patient and then modified to enhance their anti-cancer properties, before being transferred back to the patient through their veins.

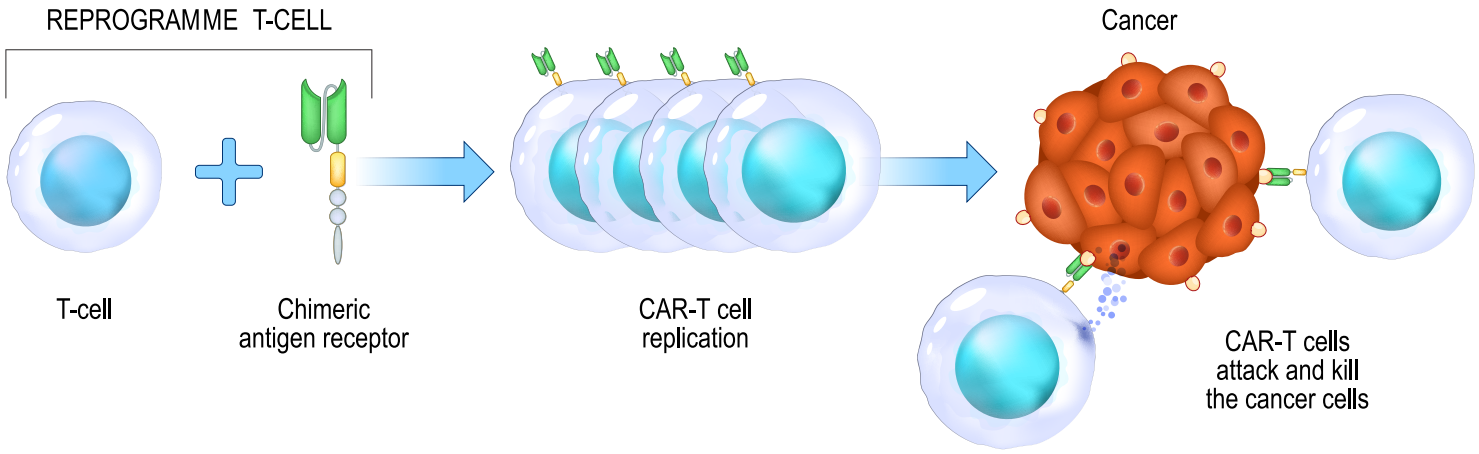
Current CAR-T therapies predominantly rely on the patient's own alpha-beta (αβ) T cells, the major population of T cells in the peripheral blood.

One of the strategies to enhance anti-cancer function of T cells is to modify the cells with a chimeric antigen receptor (CAR). CAR is an artificially engineered receptor that binds to a molecule (called an antigen) on cancer cells. In this way, T cells modified with CAR (CAR-T cells) can selectively target cancer cells carrying that specific antigen. CAR-T cells are now commonly used in ACT for B-cell malignancies, cancers which originate from the immune B-cells. This strategy is called CAR-T therapy.

Current CAR-T therapies

Current CAR-T therapies predominantly rely on the patient's alpha-beta (αβ) T cells, the major population of T cells in the peripheral blood. However, it is not suitable to use donor's αβ T cells to generate CAR-T therapies due to the risk of life-threatening graft versus host disease (GvHD), in which donor's αβ T cells ('the graft') attack healthy cells in the patient (the 'host') after infusion.

CAR-T cell therapy



Chimeric antigen receptor (CAR)-T cell therapy is a type of adoptive cell therapy (ACT) that uses CAR-modified T cells to specifically target cancer cells.

Such risk arises with donor's αβ T cells because their T-cell receptors (TCRs) may recognise host's histocompatibility complex (MHC). MHCs are fairly unique to each person. Without MHC matching between the donor and the host, GvHD is a common risk while administering αβ T cells from the donor into the host (allogeneic use). Such reliance on the patient's own αβ T cells restricts the application of current CAR-T therapy to a small pool of patients.

CytoMed aims to create novel cell-based immunotherapies for the treatment of human cancers.

CytoMed's CAR-γδ T cells

CytoMed Therapeutic Limited uses donor's gamma-delta (γδ) T cells instead of the patient's own αβ T cells to generate CAR-γδ T cells for cancer treatment. γδ T cells represent a small population of T cells (1–5%) that are an attractive choice for treatment for two reasons: they can recognise cancer cells even without modification, and they don't recognise MHC, and thus pose no risk of GvHD in allogeneic use. However, it is challenging to attain the large numbers of γδ T cells required for treatment purposes.

To resolve this, CytoMed has developed a method that allows clinical-scale expansion of γδ T cells from a small volume of donor peripheral blood. The expanded γδ T cells are then modified by incorporating a CAR to target NKG2D ligands, a type of stress-induced cancer antigen. Such CAR-γδ T cells can recognise a wide range of cancers, as demonstrated in preclinical in vitro and in vivo studies.

At CytoMed's GMP facility, this CAR-γδ T cell technology has now been successfully translated into an investigational therapeutic product. The company received approval in 2023 from the Health Sciences Authority (HSA) in Singapore to conduct a Phase I clinical trial for this donor blood cell-based product.

> **CytoMed's donor blood cell-derived CAR-γδ T cells and iPSC-derived γδ NKT cells may potentially become an 'off-the-shelf' cell therapy catering to a large pool of patients.**

CytoMed's iPSC-derived γδ NKT cells

In addition to CAR-γδ T cells, CytoMed is also developing an induced pluripotent stem cell (iPSC)-based cell therapy product. iPSCs have unlimited self-renewal capability and the potential to be transformed into any cell type, with appropriate directed programming. Taking things a step further, CytoMed has generated a unique source of iPSCs from γδ T cells – called 'γδ T-iPSCs' – as the starting material.

For cancer treatment, immune cells such as γδ T cells and natural killer (NK) cells are invaluable therapeutic agents due to their ability to express an array of built-in receptors that naturally recognise stress-induced cancer antigens. Using γδ T-iPSCs as a starting material and with their directed differentiation protocol that promotes NK cell generation from iPSCs, CytoMed can generate a novel type of synthetic hybrid immune cells, γδ NKT cells. Importantly, their γδ NKT cells express cancer recognition receptors of both γδ T cells and NK cells – enabling them to recognise a wide range of cancers without

Personal response

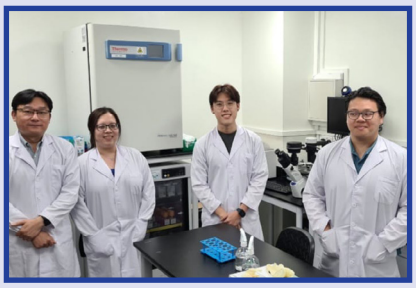
What is the next step in CytoMed's research on adoptive T cell therapy?

Currently, CytoMed are translating two exclusively licensed technologies, namely donor blood cell-based CAR-γδ T cell technology and induced pluripotent stem cell-based γδ NKT cell technology into cell therapy products. These patient blood cell-independent technologies allow the manufacturing of immune cells to recognise an array of ubiquitous cancer antigens. The resulting cell therapy products may be 'off-the-shelf', 'broad-spectrum' (indicated for a wide range of cancers, including both hematologic malignancies and solid tumors) and applicable to many cancer patients. As an important step moving towards clinical development, CytoMed began recruiting blood donors in July 2023 for a phase I trial of using CAR- γδ T cells to treat a range of advanced cancers including colorectal cancer, lymphoma, multiple myeloma, lung cancer, ovarian cancer, and hepatocellular carcinoma. Qualified donor blood cells will be used to manufacture CAR- γδ T cells for the trial at CytoMed's own GMP facility.

genetic modification or use of viral vectors, which are typically used to introduce new feature into the cells.

γδ NKT cells have proven effective in killing a wide array of cancer cell lines, including melanoma, breast, lung, and blood cancer. Live cell imaging revealed that the γδ NKT cells efficiently killed colon cancer cells in laboratory studies. This targeted killing relied on cell-to-cell contact between the γδ NKT cells and cancer cells. Further studies also revealed that all known receptors on γδ NKT cells may participate in cancer recognition. As an allogeneic cell source, CytoMed's iPSC-derived γδ NKT cells has the potential to become an 'off-the-shelf' cell therapy catering to a large pool of patients.

Details



e: enquiry@cytomed.sg
t: + 65 62507738 (Singapore)
t: + 60 73824911 (Malaysia)
w: w2.cytomed.sg
www.facebook.com/p/CytoMed-Therapeutics

Bio

Incorporated in 2018, CytoMed Therapeutics Limited is a biopharmaceutical company, spun off from A*STAR, which focuses on translating its proprietary technologies into cell-based immunotherapy for cancer treatment. CytoMed aims to create novel cell-based immunotherapies for the treatment of human cancers that will overcome clinical limitations and commercial challenges encountered by current CAR-T therapies.

Further reading

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