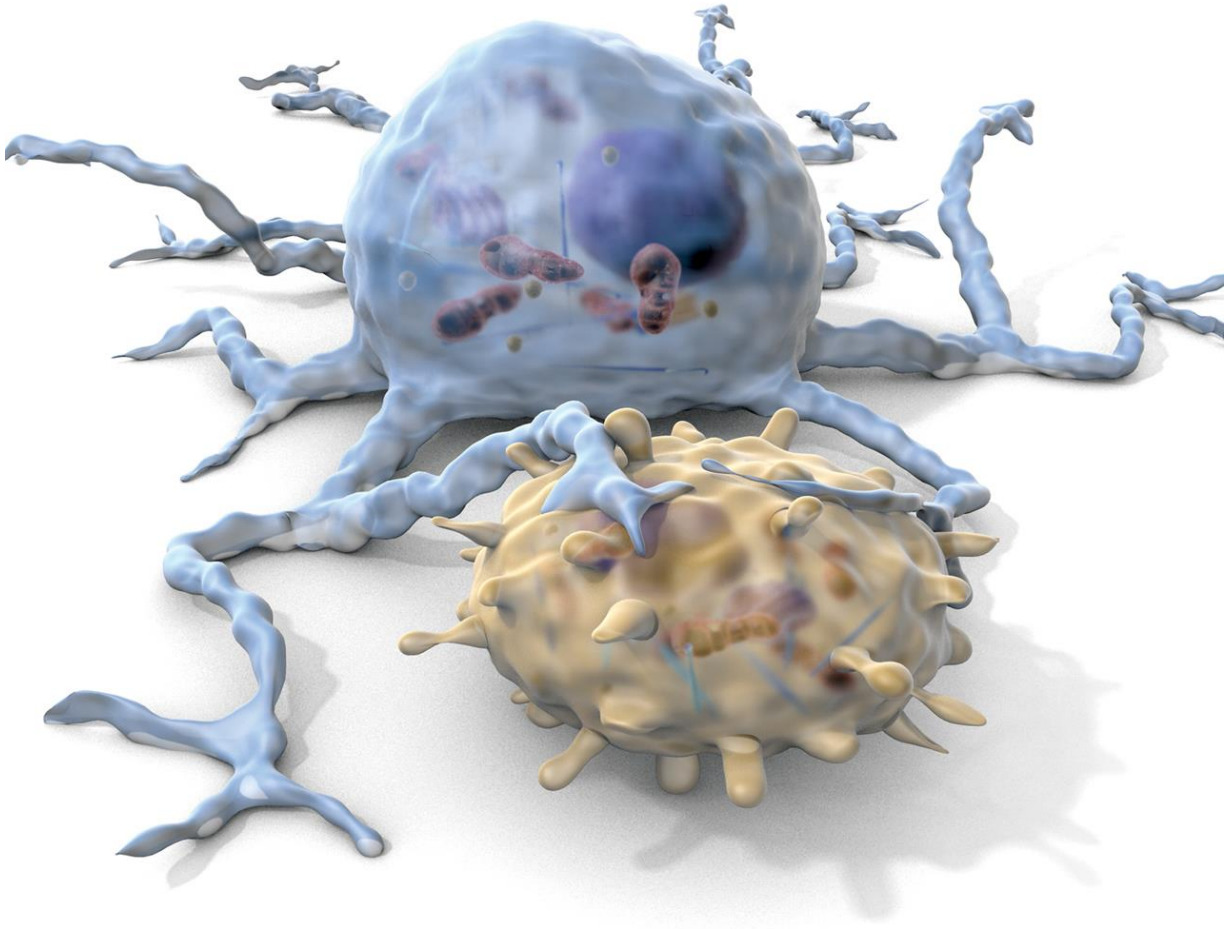


Dendritic Cell Therapy

Introduction

Dendritic cells are professional antigen-presenting cells (APCs) that can capture and process tumor-associated antigens (TAAs) [1]. Given their ability to stimulate both adaptive and innate antitumor immune responses, DCs have been used as a powerful pharmacological tool for cancer immunotherapy [2].

These cells' role is antigen presentation that is carried out through processing and presenting antigenic material to the T-lymphocytes surface [3]. The main function of immature DCs is to take tumor-derived components, while mature DCs affect the tumor-reactive CD8+ CTLs and CD4+ T cells [4].

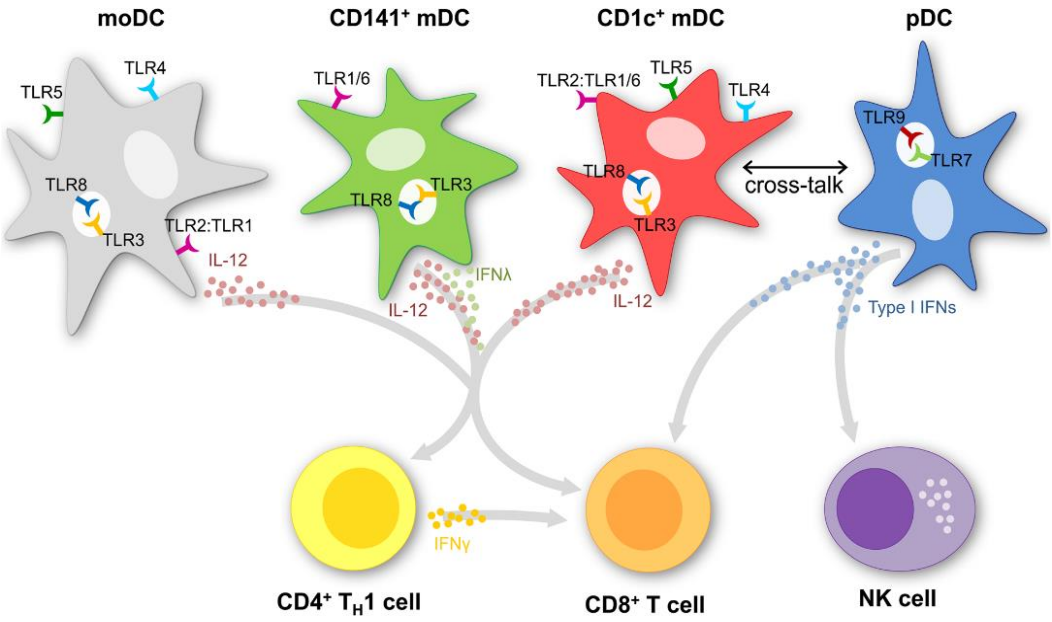


Figure 1: Dendritic cell subsets. Dendritic cells can be differentiated from monocytes (moDC), which are often used in clinical trials because of their high yield. The naturally circulating dendritic cells can now also be enriched by immunomagnetic isolation. The naturally circulating dendritic cells can further be divided in myeloid (CD141+ and CD1c+ mDC) and plasmacytoid dendritic cells (pDC). The subsets differ in function, localization, phenotype and cytokine production

Strategy

Depending on the type of DC-therapy used, long-term clinical efficacy upon DC-therapy remains restricted to a proportion of patients, likely due to lack of immunogenicity of tumor cells, presence of a stromal compartment, and the suppressive tumor microenvironment (TME), thereby leading to the development of resistance. In order to circumvent tumor-induced suppressive mechanisms and unleash the full potential of DC-therapy, considerable efforts have been made to combine DC-therapy with chemotherapy, radiotherapy or combine with another immunotherapy [5].

These combination strategies could enhance tumor immunogenicity, stimulate endogenous DCs following immunogenic cell death, improve infiltration of cytotoxic T lymphocytes (CTLs) or specifically deplete immunosuppressive cells in the TME, such as regulatory T-cells and myeloid-derived suppressor cells.

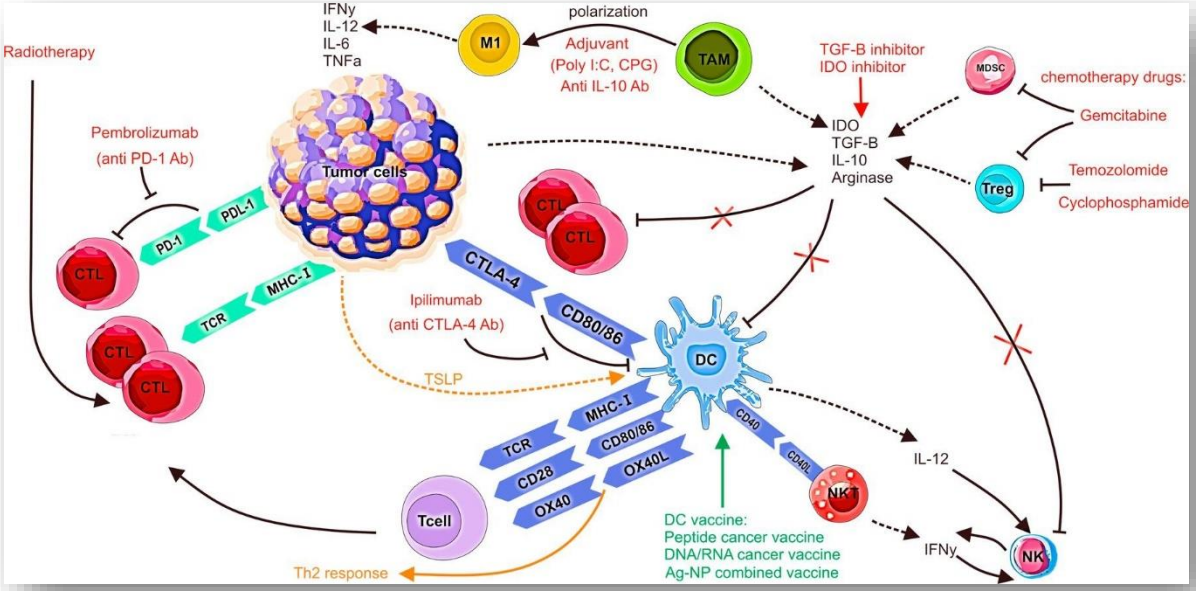
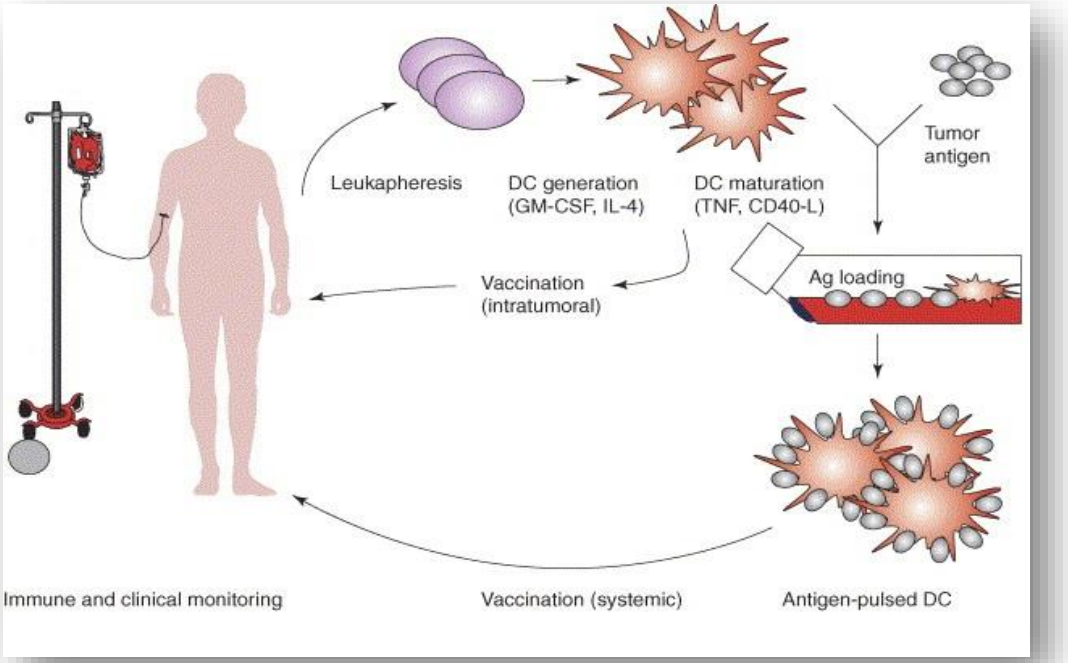


Figure 2: Immunological effects of chemotherapy, radiotherapy, and checkpoint inhibitors.

Cyclophosphamide induces ICD which enhances the recruitment, activation, maturation, and antigen uptake by DCs.

Clinical Treatment

The picture of the right illustrates the production of DCs in the laboratory. The patient's PBMC cells will be harvested by apheresis in hospital and appointed on-site local laboratory staff will transfer the PBMC sample to on-site local laboratory. In local laboratory center, they will prepare the PBMC isolation and then cryopreservation to send to Malaysia manufacturer. In Malaysia manufacturer, the cells are then cultured with IL-4 and GM-CSF. On day 5, immature DC (iDC) were pulsed with autologous tumor lysate plus keyhole limpet hemocyanin with addition of IL-4 and 25 ng/ml GM-CSF for 24 hours.



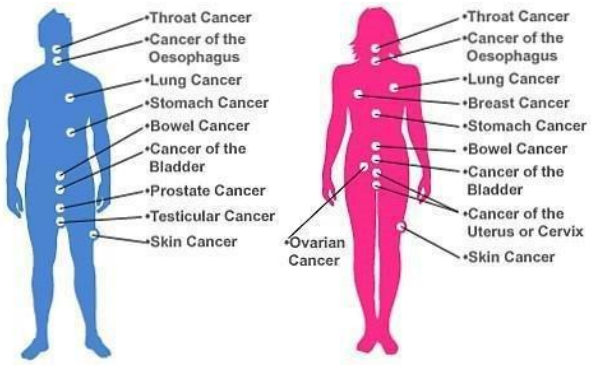
On day 6, antigen-loaded DC (aDC) were cultured with pro-inflammatory cytokine cocktail. After 24 hours, mature antigen-loaded DC (mDC, final product), were collected and frozen at the concentration of $5–6\times10^6$ viable cells/vial, and the final product of DCs will be calculated to the quantity of $1 \sim 2 \times 10^7$ dendritic cells per cycle use then suspended in 240mL normal saline. The cell products were tested according to the current Chinese Pharmacopoeia, such as microbial contamination testing being carried out to ensure the reliability, PCR based method for the mycoplasma detection to rule out contamination and quantification of bacterial endotoxin by kinetic turbidimetric methods. After passing the QC, the cell product will be cryopreserved and shipped to Hospital. After recovery in hospital, the cells are ready for infusion.

Cancer Types

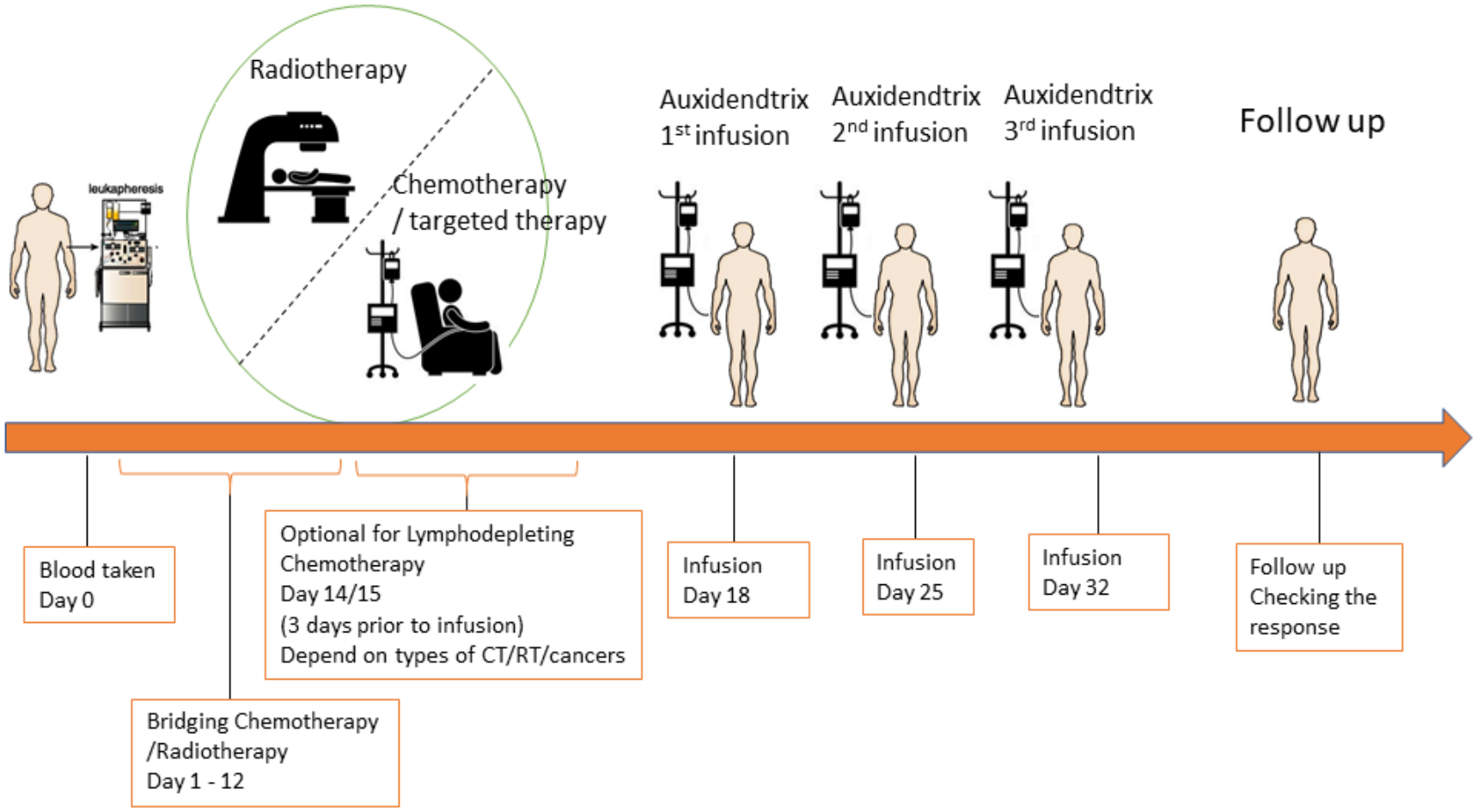
In cooperation with the Tungs' Taichung Metro Harbor Hospital, and various private hospitals in Malaysia, our group participated in application of various cell-therapies (DC, CIK, DC-CIK) in a variety of solid cancer treatment projects, that were approved by both the Ministry of Health and Welfare of Taiwan and the Ministry of Health of Malaysia.

The cell therapy applications include 22 types of stage 4 solid cancers, including the cancer types listed in the table below [ref: MOHW, Taiwan].

- Adrenal Cancer
- Biliary Tract Cancer
- Bladder Cancer
- Brain Malignant Tumor
- Breast Cancer
- Cervical Cancer
- Colorectal Cancer
- Endometrial Cancer
- Esophageal Cancer
- Gastric Cancer
- Germ Cell Cancer
- Head & Neck Cancer
- Kidney Cancer
- Liver Cancer
- Lungs Cancer
- Neuroendocrine Cancer
- Ovarian Cancer
- Pancreatic Cancer
- Prostate Cancer
- Soft Tissue Sarcoma
- Skin Cancer
- Thyroid Cancer



Treatment Flow



Infusion

For autologous use only. Patients will receive at least 3 cycles of DCs infusion with one-week intervals between each cycle. 1~2 $x10^7$ cells were suspended in 100mL normal saline and administered via intravenous infusion within 20 minutes.

The immune cell therapy program can be combined with other treatment methods, including anti-inflammatory drugs (NSAID) and antipyretic analgesics to relieve the patient's discomfort. Or combined use of radiation therapy, targeted therapy, chemotherapy, immune checkpoint inhibitor therapy, and so on to improve the overall anti-cancer efficacy. All concomitant treatment methods must be evaluated by the operating specialist's professional clinical experience, and the relevant adverse reactions of concomitant treatment should be observed at any time.

All patients were followed up after discharge, including blood routine examination and PET CT/CT screening every 3 months for the first 2 years, 6 months for the next 3 years, and yearly thereafter from the fifth year.

Possible Side Effects

According to the results of clinical trial literature, the most common adverse reactions of CIK cell therapy are mostly mild symptoms such as fever and pain. Although the frequency is incredibly low, the symptoms will resolve spontaneously without treatment. However, each patient may have special reactions (idiosyncrasy) due to individual differences and special constitutions. If nausea, vomiting, diarrhea, or shock occurs after the cell reinfusion, the cell reinfusion should be stopped and treated according to the specialist's instructions.

Adverse Effect	Descriptions
Grade 1	The operating physician needs to place the patient in a comfortable space and observe until the adverse event resolves spontaneously or gives appropriate physical support (ice compress, drinking warm water, sleep, etc.).
Grade 2	The operating physician immediately places the patient and observes whether the adverse event tends to ease or become more serious. If it tends to be relieved, physical support is given to accelerate the resolution of the adverse event; if it tends to be serious, evaluate the severity of the patient and give appropriate drug support (antipyretic, analgesic, steroid, etc.). Continue observation and drug support until the adverse event stabilizes or resolves. Suspend this course of treatment and enter the observation period and reassess whether to continue treatment after the cause is found out.
Grade 3	The operating physician must immediately take emergency measures and administer medication support (antipyretic, analgesic, steroids, pressure boosters, electrolyte infusion... etc.) according to the patient's symptoms. Arrange to be hospitalized and continue treatment and slow medication reduction until the symptoms are completely resolved. The patient withdraws from this course of treatment, terminates the cell reinfusion, and arranges for routine medical care for the patient.
Grade 4	The operating physician must immediately be sent to the emergency department to take first aid measures and provide life support (intratracheal intubation, steroids, pressure boosters, electrolyte infusion, etc.) according to the patient's symptoms. Arrange to the intensive care unit as soon as possible and continue treatment until the symptoms are completely stable or resolved. The patient withdraws from this course of treatment, terminates the cell reinfusion, and arranges for routine medical care for the patient.

Good Tissue Practice Lab

The facility is designed with regulations that are stricter than any Good Tissue Laboratory (GTP) regulations to avoid risks of environmental contamination including multiple gowning procedures (primary and secondary changing rooms, biologically safety areas, and limited access to qualified persons. The facility complies with the FDA high standard secondary dressing facility.

24 hours-Uninterruptible Power System-maintaining cells under carefully controlled conditions.

- **The lab was equipped with independent power generators.**
- **UPS battery backup supplies for all lab instruments.**

SITE SPECIFICATIONS

It has a cleanliness level of 10,000, a "positive pressure, constant humidity, constant temperature" high-standard dust-free independent laboratory, and a complete control mechanism, which can provide various process facilities for cell therapy.

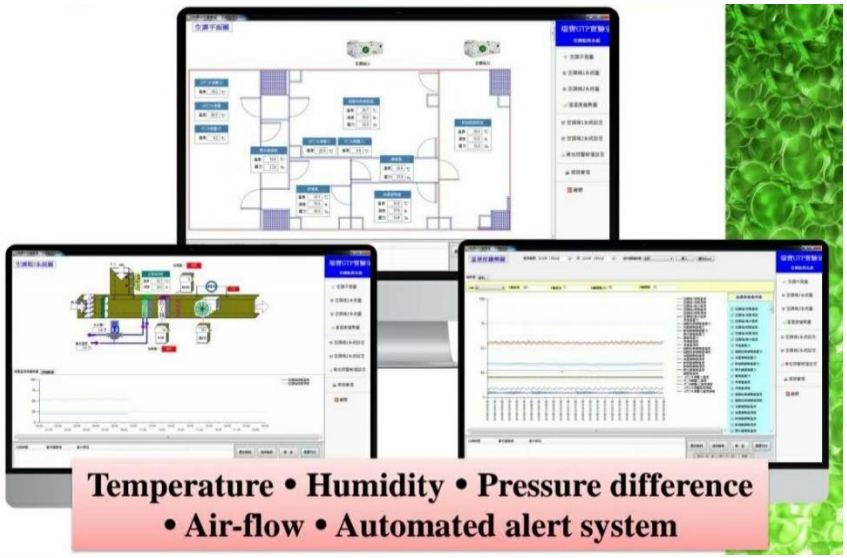
CLEANLINESS

With a cleanliness of 10,000 and a complete control mechanisms, it can provide various process facilities required for cell therapy.

STRICT REQUIREMENTS

Adhere to the use of high-quality manufacturer-sourced reagents, high-end equipment, and full-process serum-free culture to improve the effectiveness and safety of human cell tissue operations. Strict operation procedures, manufacturing procedures, storage conditions, effective time and records are established for the acceptance/feeding of human cell tissues, acceptance or return, distribution, and destruction or disposal.

Good Tissue Practice Lab

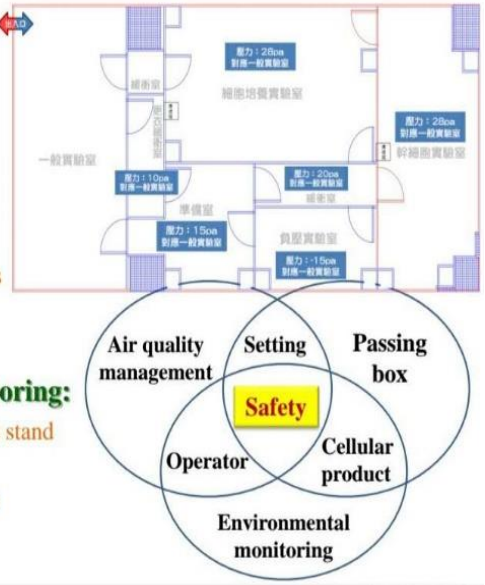


GTP requirements:

- Requirements for facilities
- Environmental control
- Equipment
- Supplies & Reagents
- Recovery
- Processing and Process controls
- Labelling controls
- Storage

Air qualification and monitoring:

- Air-handling system in separate stand alone units
- Filter-based stand alone system



Strict standards for final products testing according to the current Chinese Pharmacopoeia.

Bacteria
Microbial contamination testing being carried out to ensure the reliability.

Mycoplasma
Validation of a PCR-based method for the mycoplasma detection to rule out contamination.

Endotoxin
Quantification of bacterial endotoxin by turbidimetric technique.

Cryopreservation
Cellular products can be frozen and stored. It's important to be able to track each product.

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Why Vamos?

Our Focus

We invent and produce new technology and new substances for treatment of cancers, viral infections, antibiotic resistant bacterial infections, and other incurable diseases.

Our Results

Our products achieve results in treatments of many incurable diseases for which treatments are not available or no results can be reached.

Our Prices

The costs of our cancer immunotherapies are the lowest in the industry and significantly lower compared to any other competitor, while at the same time, our results are second to none.

THANK YOU

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