

DEFINING MED

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Cell Therapy

Cell Therapy: A Growing Revolution

Regenerative Medicine to Improve Patient Care

A Paradigm Shift in Combating Sarcopenia

Revolutionising Cancer Treatment with CAR T-Cell Immunotherapy

Advancing Cartilage Regeneration for Chondral Defects of the Knee

Bringing Cell Therapeutics from Clinical Trials to Bedside

PLUS

Minimally Invasive Breast Surgery for Improved Aesthetic Outcomes



Cell Therapy: No Longer Science Fiction but a Growing Clinical Reality

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Primary care physicians are often the first to see patients who suspect they have cancer, heart disease, neurological disorders and more. While the care of these patients is usually referred to specialists, general practitioners may find it useful to discover how cell therapy may now be employed to treat complex diseases in some cases when conventional treatment does not work.

WHAT IS CELL THERAPY?

Cell therapy is an exciting new field of medicine, where cells are used as living drugs that will continue to grow in the patient to exert and amplify their beneficial effects for the long term. This has been a big revolution in medicine and many patients around the world have been benefitting from the use of cells for treatment.

There are two main categories of cell therapy:
cellular immunotherapy and **regenerative medicine**.

1

In **cellular immunotherapy**, immune cells are grown and 'trained' to fight diseases like cancer and infectious diseases by resetting the immune system and/or through genetic modifications of the immune cells.

2

Cellular regenerative medicine is a fast-growing area of medicine that restores, repairs or replaces damaged cells, tissue or organs in the body. This is particularly relevant for progressive disease conditions such as heart disease, eye degeneration, and neurological and musculoskeletal disorders.

WHAT CONDITIONS CAN BE TREATED WITH CELL THERAPY?

The use of cell therapy is growing and diversifying. Several new cell therapy products have been approved by the United States Food and Drug Administration (FDA) in recent years, with more to come.

Haematological conditions

The **chimeric antigen receptor T cell (CAR T cell)** is one such example. These are patient-derived T cells that undergo genetic modification to express an artificial T cell receptor against an antigen that is expressed on the surface of cancer cells.

Currently, there are five FDA-approved CAR T cells for use in haematological conditions such as:

- Acute B-cell lymphoblastic leukaemia (ALL)
- Diffuse large B-cell lymphoma (DLBCL)
- Mantle cell lymphoma (MCL)
- Multiple myeloma (MM)

Patients must have received at least two lines of treatment and not responded before they can receive CAR T-cell therapy.

Age-related diseases and chronic conditions

Cellular regenerative medicine has been applied in the treatment of age-related diseases and chronic conditions, for example:

- **Regenerated blood cells** are used to treat bone marrow and blood disorders of the bone marrow
- **Stem cells** are used to treat eye diseases like corneal disease
- **Regenerated skin cells** are used for acute and chronic wound healing like burns

Other applications

In 2016, the FDA approved the use of an autologous cellularised scaffold product for the repair of symptomatic cartilage defects of the knee.

Regenerative medicine cell therapy applications are also being studied for future clinical use in heart disease, muscle wasting, and diseases like Parkinson and Alzheimer's.

WHO IS ELIGIBLE FOR CAR T-CELL THERAPY IN SINGAPORE?

Singapore General Hospital was the first site in Southeast Asia to be approved for the FDA-registered CAR T-cell therapy for ALL and DLBCL. Many of its patients receiving CAR T-cell therapy have attained control of leukaemia and lymphoma, when they were previously resistant to all forms of chemotherapy.

Current indications	Upcoming indications	Potential future indications (in development)
<ul style="list-style-type: none"> → Patients with relapsed and refractory DLBCL after at least two lines of therapy → Patients with ALL that have failed conventional chemotherapy 	<ul style="list-style-type: none"> → Patients with relapsed and refractory MM that have failed multiple lines of treatment 	<ul style="list-style-type: none"> → Patients with earlier stages of the aforementioned ailments → Patients with other malignancies (including solid tumours)

BUILDING A PIPELINE OF CELLULAR AND REGENERATIVE THERAPIES

Launched earlier this year in May 2021, the **SingHealth Duke-NUS Cell Therapy Centre (SDCT)** will prepare clinical teams for the cell therapy revolution.

Launched concurrently with SDCT is the **SingHealth Duke-NUS Regenerative Medicine Institute of Singapore (REMEDIS)**, which will harness the potential of regenerating diseased cells, tissue and even organs to tackle age-related diseases and chronic conditions.

The establishment of REMEDIS and SDCT sets up a bench-to-bedside pipeline – REMEDIS will develop research, regenerative therapies and tools, while SDCT will bring the treatments directly to patients by taking these into clinical trials and clinical applications that can benefit patients.

SDCT will also focus on training and enabling clinical teams to bring to patients the best that cell therapy has to offer.

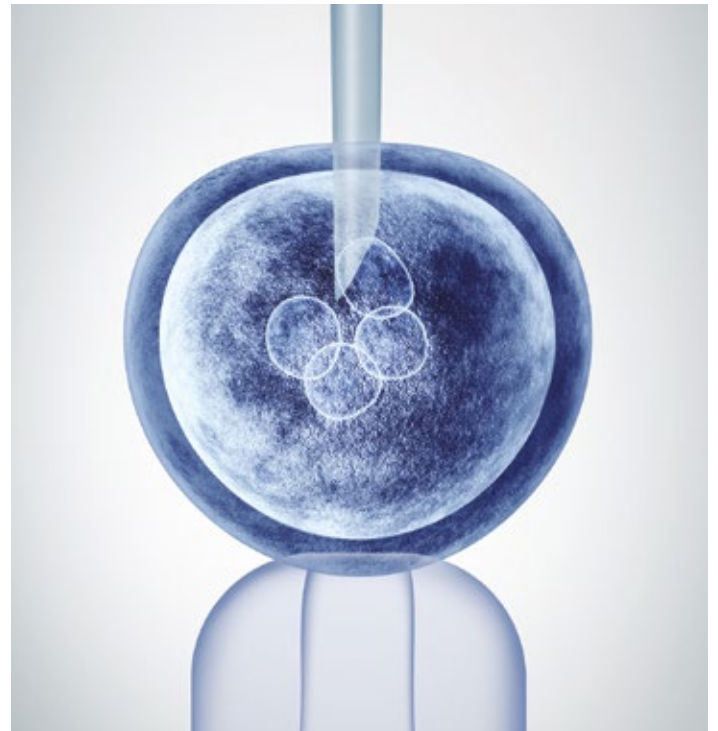
FUTURE APPLICATIONS ON THE SINGHEALTH CAMPUS

Applying cell therapy to overcome limitations in existing treatment options

With support from the National Research Foundation Singapore, applications of cellular regenerative medicine on the SingHealth campus will kick off with a research study led by clinician-scientists from the SingHealth Duke-NUS Academic Medical Centre.

Professor William Hwang, Medical Director of the National Cancer Centre Singapore and Lead Principal Investigator of the study, with Team Principal Investigators Professor Karl Tryggvason and Assistant Professor Tay Hwee Goon from the Cardiovascular and Metabolic Disorders Programme at Duke-NUS Medical School, will develop cellular therapy products for three disease areas:

1. **Age-related macular degeneration**
2. **Ischaemic cardiomyopathy**
3. **Blood cancers**



Due to the limitations of existing therapies, the research team is working towards safe and effective treatments for patients affected by these conditions.

Developing stem cells for regenerative medicine

Professor Tryggvason, a world-renowned researcher from Duke-NUS, is a leader in laminin technology. Laminins form the basement membrane on which cells grow in many tissues and, in tissue culture, they give a road map to cells to tell them what kind of cells they should become.

His team has been able to produce exciting functioning cells that seem to work in animals to repair cells of the heart, eye and skin. The research team intends to enhance this process with small molecules and to extend the use of these laminins for bone marrow diseases.

If the development of cellular therapy products and pre-clinical models is successful, the team has plans to conduct clinical trials and commercialise the products. In addition, the team will document and chart the process and development of the products with scientific studies and patents, which will add to knowledge about regenerative medicine that can ultimately be used in biomedical and clinical applications to improve patient care.

ADVISING PATIENTS ABOUT CELL THERAPY

Not all activities in cell therapy and regenerative medicine are based on solid science, and we need to be responsible gatekeepers to only adopt those which have good clinical and pre-clinical evidence.

A lot of this work is still in the research phase and not yet in clinics, but cell therapy is fast becoming a viable treatment option and no longer science fiction.

THE ROAD AHEAD

In Singapore, there is growing interest in cell-and-tissue-based products as potential treatments for a variety of diseases. The government has taken measures to advance cell therapy through the establishment of a local Good Manufacturing Practice (GMP) facility, the Advanced Cell Therapy and Research Institute, Singapore (ACTRIS), and investing \$80 million of national funds in cell therapy research.

The recently implemented local regulatory framework for cell, tissue and gene therapy products (CTGTP) is another measure to allow the use of these therapies in Singapore with guidance.

Medical professionals who would like more information about the available cell therapies, please direct your enquiries to sd.cell.therapy@singhealth.com.sg.

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GPs can contact the **SingHealth Duke-NUS Cell Therapy Centre** at sd.cell.therapy@singhealth.com.sg to know more about the available cell therapies and clinical trials on the SingHealth campus, or scan the QR code for more information.



A New Approach to Treating Cancer – Chimeric Antigen Receptor (CAR) T-Cell Immunotherapy

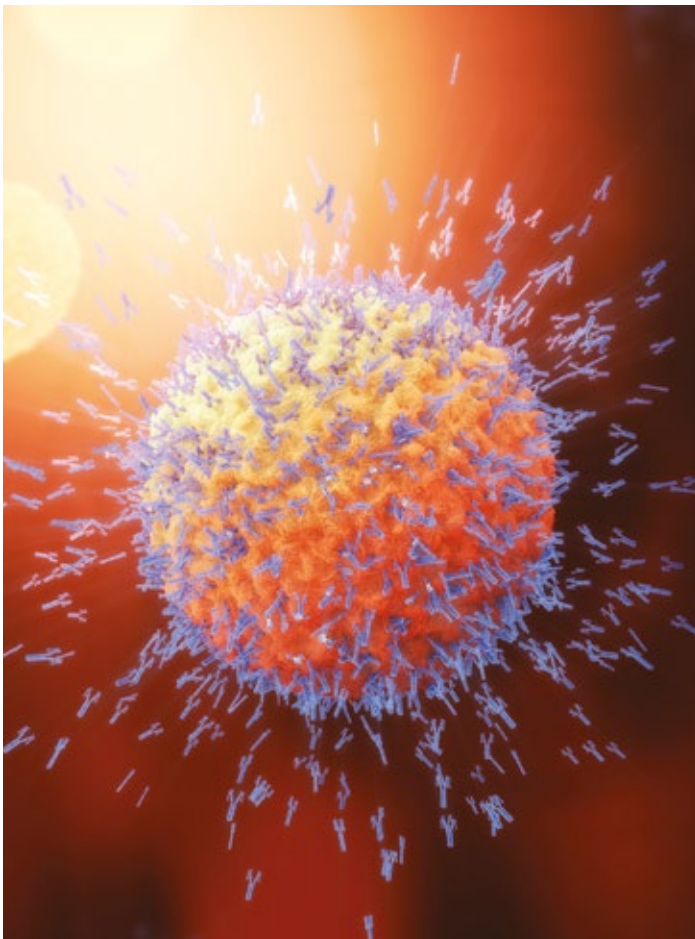
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With rising cancer incidence and improvements in patient survival outcomes through novel therapies such as cellular immunotherapy, general practitioners are poised to take on an increasing role in partnering haematologists or oncologists in joint cancer survivorship programmes. Find out more about CAR T-cell therapy as a novel approach in the treatment of haematological malignancy and the care pathways surrounding its delivery.



INTRODUCTION

The evolving field of cellular immunotherapy is revolutionising the cancer treatment landscape.

Chimeric antigen receptor (CAR) T-cell therapy is a form of adoptive T-cell therapy that has been recently introduced in the treatment armamentarium of haematological malignancies. It involves ex vivo engineering of the patient's autologous T cells to equip them with receptors targeting specific antigens on cancer cells, and subsequently infusing these genetically modified T cells back into patients to bring about cancer-directed cytotoxicity.

Here we will focus on the patient journey, using **CAR T-cell therapy** as an example of cellular immunotherapy for diffuse large B-cell lymphoma (DLBCL), and elaborate on the role of general practitioners (GPs) as cell therapies become more common in clinical practice.

PREVALENCE OF DLBCL IN SINGAPORE

In Singapore, tisagenlecleucel (Kymriah), an anti-CD19 CAR T-cell therapy, is currently approved and available for use in young adults (≤ 25 years) with relapsed/refractory (R/R) acute B-cell lymphoblastic leukaemia (B-ALL) and adults with DLBCL.

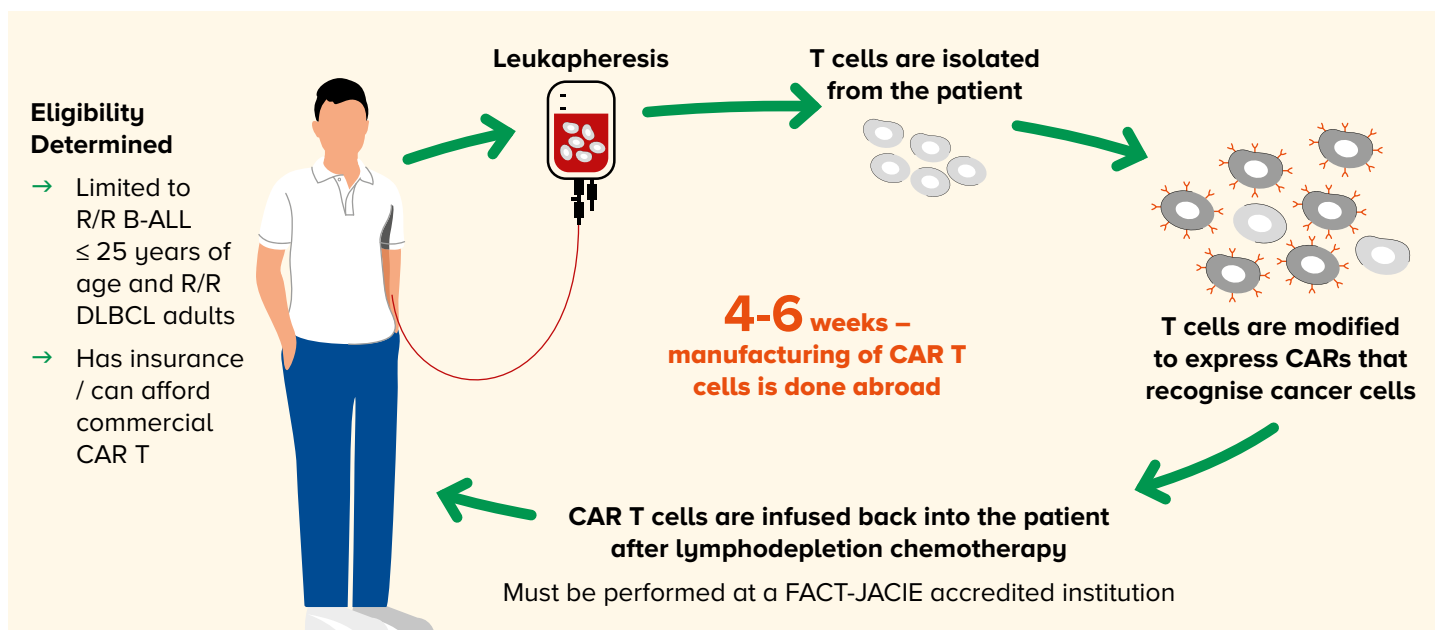


Figure 1 The CAR T workflow at the Singapore General Hospital Department of Haematology

DLBCL is the most common form of aggressive lymphoma in Singapore. The median age of DLBCL patients locally is 60-65 years. According to the World Health Organization's guidance on classifying cancers, DLBCL accounts for 30-40% of newly diagnosed cases of non-Hodgkin lymphoma globally.

Early symptoms of DLBCL

It is paramount that patients who are suspected to have DLBCL are referred immediately. Early symptoms of DLBCL include lumps in the neck, armpits or groin. Some patients may not show any obvious symptoms except fevers that may persist and unexplained weight loss.

WHO CAN BENEFIT FROM CAR T-CELL THERAPY?

Patients diagnosed with DLBCL will undergo standard of care therapy with an anti-CD 20 monoclonal antibody and chemotherapy. The majority will respond and go into remission. However, 30-40% will relapse and among those who do, up to 50% may still be refractory to salvage therapies with dismal outcomes.

CAR T-cell therapy offers an alternative form of treatment for such patients with a complete remission rate of 40%.

However, the process of delivering and administering CAR T-cell therapy to a patient is complex, as illustrated in **Figure 1**.

Even if patients meet the criteria for CAR T-cell therapy, they still need to have a consultation with a haematologist to ensure that they would benefit from this therapy, and are willing to accept the toxicities associated with it.

CELLULAR IMMUNOTHERAPY AT THE SINGAPORE GENERAL HOSPITAL DEPARTMENT OF HAEMATOLOGY

At Singapore General Hospital (SGH), the Department of Haematology is accredited to administer cell therapy products to patients. The hospital is equipped with the appropriate infrastructure, as well as a multidisciplinary team comprising trained individuals, to care for these patients.

Currently, every patient who might benefit from CAR T-cell therapy is presented at our Haematology Lymphoma Tumour Board and subsequently at our Haematopoietic Cell Therapy and Transplant Programme (HCTTP) meetings.

We have treated ten patients with CAR-T cell therapy since last year at SGH.

THE CELLULAR IMMUNOTHERAPY PATIENT JOURNEY

① Counselling on the treatment plan

The patient will need to be counselled on the various steps:

- 1 The process of **leukapheresis** to obtain the T cells from the patient for manufacturing of CAR T cells
- 2 The possibility of receiving **bridging therapy** while waiting for the CAR T cells to arrive – this could comprise more immunochemotherapy, radiotherapy or a combination
- 3 The admission for **lymphodepletion chemotherapy** before the infusion of CAR T-cell therapy and the toxicities
- 4 The discharge planning and follow-up

② Managing the patient's emotions

The emotions that the patient experiences during this whole process cannot be overemphasised. There is much anxiety and expectation, and it is paramount that the clinician spends time explaining this complex process to them.

It is challenging for the patient to comprehend how these CAR T cells are manufactured with a turnaround time of six weeks, and to accept the unique toxicities associated with CAR T-cell therapy.

③ Understanding and managing acute toxicities

These therapies are associated with unique acute toxicities of **cytokine release syndrome (CRS)** and **neurological toxicity**, also referred to as CAR-related encephalopathy syndrome (CRES) or immune effector cell-associated neurotoxicity syndrome (ICANS), that are not typically seen with traditional anticancer therapies.

● Cytokine release syndrome (CRS)

CRS is the most common acute adverse event associated with CAR T-cell therapy.

CRS is a systemic inflammatory response triggered by the release of cytokines by CAR T cells following

their activation upon tumour recognition in vivo. The CAR T cells also activate bystander immune cells such as macrophages, which in turn release inflammatory cytokines and contribute to the pathophysiology of CRS.

● **Presentation**

CRS typically manifests with constitutional symptoms of fever, myalgias, rigours, fatigue and loss of appetite, but can lead to multiorgan dysfunction in more severe cases.

● **Management**

CRS is completely reversible if managed appropriately. Serum IL-6 levels have been shown to correlate with the severity of CRS, and the blockade of IL-6 with tocilizumab, an anti-IL-6 receptor antibody, can reverse CRS.

● **Immune effector cell-associated neurotoxicity syndrome (ICANS)**

ICANS is less well-understood than CRS. Like CRS, cytokines, chemokines, and the degree of CAR T cell expansion have been associated with more severe neurotoxicity.

● **Presentation**

It typically presents as a toxic encephalopathy with word-finding difficulty, aphasia and confusion but can progress in more severe cases to depressed levels of consciousness, comas, seizures, motor weakness and cerebral oedema.

● **Management**

Because of the limited understanding of the pathophysiology, ICANS is primarily managed with supportive care for low-grade toxicity, and corticosteroids are frequently used for more severe grades. Like CRS, ICANS is also completely reversible in most patients and tends to have a self-limited course.

● **Other toxicities**

In addition, delayed toxicities such as prolonged cytopenias, risk of opportunistic infections, and on-target but off-tumour effects such as B-cell aplasia are observed with anti-CD19 CAR T products.

THE GP'S ROLE AND RESPONSIBILITY IN THE ERA OF CELL THERAPY

Not all cell and gene therapies have gained FDA approval. Many are still in the pre-clinical stage of development and are required to undergo the rigours of clinical trial before they are truly proven to be safe and efficacious.

However, with such limelight on cell therapy, patients are always attracted to new therapies and curious to understand if they are available in Singapore. Unfortunately, this is often the response of desperate patients – those who have failed line after line of therapies – and they often fall prey to these unproven cell therapies.

Educating and referring patients

As a GP, you may encounter circumstances where your opinion is sought regarding cell therapies. Your role will thus be paramount in educating the patient and their relatives that unproven cell therapies may not just be costly, but can also have severe devastating effects on their health even resulting in death.

You may also play a critical role in directing the patient to specialist centres in the event of any ambiguity.

Working with specialists for shared care Integrating care

The patient journey may also be emotionally challenging and physically demanding. Here, there can be greater integration of care between the GP and specialist in the many pre- and post- treatment visits as illustrated in *Figure 2*.

Establishing channels of communication

The channel of communication between GPs and specialists should be well established such that the patient is not left to communicate with both parties independently.

Patients should be assured that the GP is aware of what is happening at the hospital, and is confident in providing the extra support in the community and advising the patient to go to the hospital when appropriate.

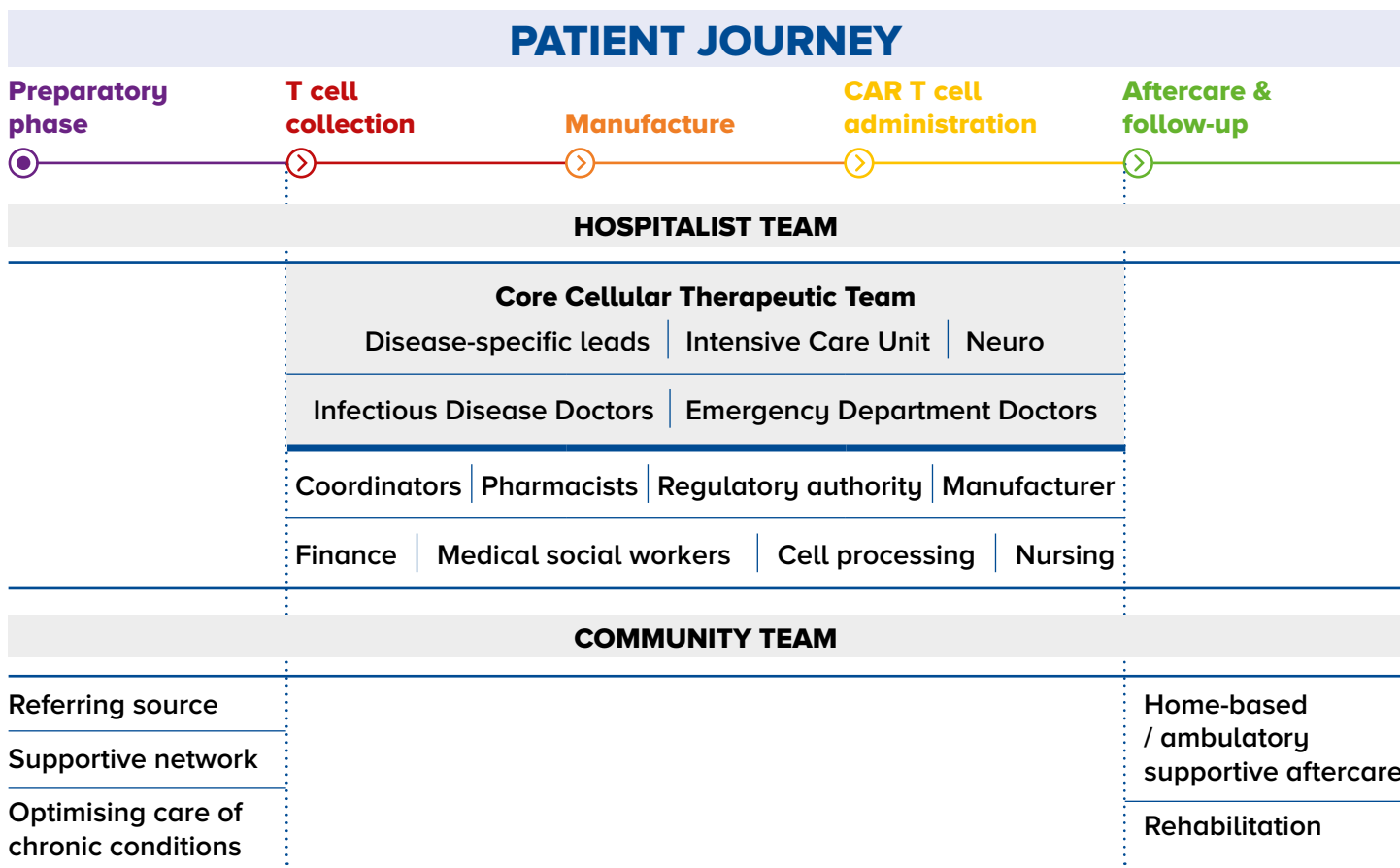


Figure 2 The patient journey through a shared care programme

THE FUTURE OF CELL THERAPIES

Current FDA-approved therapies

There are currently five FDA-approved second generation CAR T-cell therapies as shown in **Table 1**.

The current drug labels are for **B-ALL, B-lymphoproliferative disorders** and **multiple myeloma**. Current approved CAR T-cell therapies are autologous in nature and for use in the R/R setting.

Many other CAR T-cell therapies are being investigated in ongoing clinical trials, and we anticipate others to be approved in future for other haematological cancers and solid tumours.

‘Off-the-shelf’ CAR T-cell therapy products

There are also ongoing clinical trials looking at ‘off-the-shelf’ CAR T-cell therapy products – where instead of using autologous T cells for the manufacturing of these products, researchers and clinicians are using other **immune cells from healthy donors** such as natural killer cells (NK cells) and gamma delta T cells (GDT cells).

The rationale for doing so is to make this form of therapy more accessible for all patients with a faster turnaround time, and hopefully be able to provide starting cells that are ‘healthier’ as they are not from the patient.

There is also much research activity on how the CARs can be further modified to make them more efficient in killing cancer cells and to make them safer with less risk of CRS and ICANS.

FDA-APPROVED CARs	INDICATIONS	PIVOTAL TRIALS	RESULTS
TISAGENLECLEUCEL (KYMRIAH) 2017/2018	B-ALL (R/R), DLBCL (R/R)	JULIET Phase II	ORR 50% (40% CR, 12% PR), OS at 12 months 95% (in patients with CR)
AXICABTAGENE (YESCARTA) 2017	Large B-cell lymphoma (R/R) (primary mediastinal, DLBCL, high grade B-cell lymphoma)	ZUMA 1 Phase I/II	ORR 83% (58% CR) OS at 24 months 51% (median OS not reached)
BREXUCABTAGENE AUTOLEUCEL (TECARTUS) 2020	Mantle cell lymphoma (R/R)	ZUMA 2	ORR 87% (62% CR)
LISOCABTAGENE MARALEUCEL (BREYANZI) 2021	Large B-cell lymphoma (R/R)	TRANSCEND	ORR 73% (54% CR)
IDECABTAGENE VICLEUCEL (IDE-CEL; BB2121) 2021	R/R multiple myeloma	KarMMa Phase II study	ORR 73% (33% CR)

Table 1 FDA-approved second generation CARs and their respective indications. These are all autologous-derived cell therapy products. The first four CARs target the CD19 antigen while the fifth targets the B-cell maturation antigen.

ALL: acute lymphoblastic leukaemia, **DLBCL:** diffuse large B-cell lymphoma, **R/R:** relapsed/refractory, **ORR:** overall response rate, **CR:** complete response, **PR:** partial response, **OS:** overall survival

CONCLUSION

It is evident that immune cell therapy is here to stay and the potential to use these therapies for other diseases is promising. In Singapore, this is a new paradigm in medicine and it is important for all GPs to be aware of this shift – where we are no longer just using pills to treat patients, but also using living cells to cure them of diseases.



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Dr Chen Yunxin is a Consultant Haematologist at Singapore General Hospital, and Co-Lead (Education) and Clinical Deputy Lead (Adult Blood Cancer) at the SingHealth Duke-NUS Cell Therapy Centre. She specialises in the care of patients with multiple myeloma and lymphoproliferative disorders.

She completed her Health Manpower Development Plan on immunotherapy at the Memorial Sloan Kettering Cancer Center where she was involved in developing novel cellular therapeutics for treatment of multiple myeloma as well as myeloma CAR T cell clinical trials. She works with a dedicated team of physicians and allied health professionals in the Haematopoietic Stem Cell Transplant Programme to deliver CAR T cells to patients as well as to develop outpatient transplant services.



GPs can contact the **SingHealth Duke-NUS Cell Therapy Centre** at sd.cell.therapy@singhealth.com.sg to know more about the available cell therapies and clinical trials on the SingHealth campus, or scan the QR code for more information.



Restoring Function, Embracing Life: Regenerative Medicine to Improve Patient Care

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With the ageing local and global population, regenerative medicine is growing in both interest and importance. From heart and eye diseases to Alzheimer's, find out how the ongoing research and innovation work at the SingHealth Duke-NUS Regenerative Medicine Institute of Singapore (REMEDI) promises to improve medical treatments and patient outcomes.

INTRODUCTION

What is regenerative medicine?

Regenerative medicine is the science of developing therapeutics and tools to restore diseased tissues and organs.

It includes gene therapies, cell therapies, tissue-engineered products and small molecules intended to augment, repair, replace or regenerate organs, tissues, cells, genes and metabolic processes in the body.

Why is it important?

Regenerative medicine is of particular importance to the ageing global population. In Singapore, the median population age has doubled over the last five decades, leading to an increase in age-related diseases of the heart, neurons and eyes, and even cancers.

Effective and accessible clinical care for these debilitating age-related conditions could also mean savings of billions of dollars that would otherwise be used to foot the bills for chronic medical care and work productivity losses.



A Hub of Regenerative Medicine:

The SingHealth Duke-NUS Regenerative Medicine Institute of Singapore (REMEDI^S)

The SingHealth Duke-NUS Regenerative Medicine Institute of Singapore, otherwise known as **REMEDI^S**, was established at the SingHealth Duke-NUS Academic Medical Centre as a global centre of excellence for basic and translational research in regenerative medicine.

Singapore is equipped with extensive multidisciplinary research hubs and clinical infrastructure that are essential for cutting-edge research in regenerative

medicine. By consolidating and focusing these resources through the establishment of REMEDI^S, Singapore could soon be at the forefront of innovating and delivering regenerative medicine products to patients in the region and beyond.

REMEDI^S will work towards its vision of 'Restoring Function and Embracing Life' in collaboration with multidisciplinary research hubs and local clinical groups.

Areas of focus for REMEDI^S include regenerative therapies for:

					
Ischaemic heart disease	Sarcopenia	Neurodegenerative diseases (e.g., Alzheimer's and Parkinson disease)	Age-related eye diseases	Bone marrow disorders	Burns

Ongoing work by REMEDI^S to advance regenerative medicine includes:



CARDIOVASCULAR REGENERATION FOR CARDIOMYOPATHY

The Cardiovascular Regeneration Programme focuses on heart disease, an important cause of mortality and morbidity.

Professor Tryggvason of Duke-NUS Medical School and his team have **established the use of extracellular matrix proteins to grow human cardiomyocytes from pluripotent stem cells.**

These cardiovascular progenitors, when implanted in pigs with myocardial infarction, rescued infarcted hearts, functioned normally and most importantly did not cause ventricular arrhythmia, a common problem in other competing technologies.

The team has obtained a grant from the National Research Foundation to translate these therapies to clinical applications with clinicians from the National Heart Centre Singapore. If successful, this could reduce the need for heart transplantation, which is limited due to the lack of donors.



SKELETAL MUSCLE REGENERATION FOR SARCOPENIA

The Skeletal Muscle Regeneration Group focuses on sarcopenia, a skeletal muscle wasting disease, which is a poorly understood threat to the health span, mobility and quality of life of the ageing population. There is currently no cure.

The team has successfully identified a cause and potential treatment for sarcopenia associated with cancer and now sets its sights on addressing skeletal muscle wasting associated with ageing and other diseases like liver cirrhosis and renal failure.



NEURAL REGENERATION FOR ALZHEIMER'S AND PARKINSON DISEASE

Professor Zhang Suchun of Duke-NUS Medical School is a leader in successfully generating different types of healthy neurons from pluripotent stem cells that could be used to replace diseased neurons.

Dr Tan Eng King of the National Neuroscience Institute has also pioneered the use of stem cells to treat

Parkinson disease. While much of this research is still in the pre-clinical stage, success could lead to new treatments for Alzheimer's and Parkinson disease.



EYE REGENERATION FOR AGE-RELATED EYE DISEASES

Sight is probably the most powerful sense of the human body. Unfortunately, there are at least 2.2 billion people worldwide who have impaired vision or blindness. The majority are over the age of 50.

The two leading causes of age-related blindness are Fuchs' endothelial corneal dystrophy and age-related macular degeneration.

Professor Jodhbir Mehta of the Singapore National Eye Centre has **pioneered a robust culture system for human corneal endothelial cells to treat age-related corneal blindness**, and was also the first to identify the location of corneal endothelial progenitors. In addition, the team of scientists has developed and patented a novel photoreceptor differentiation method.



BONE MARROW REGENERATION FOR BLOOD CANCERS

Bone marrow failure can occur because of ageing, genetic conditions, immune dysfunction or as a pre-leukaemia disorder. It is usually thought of as a hematopoietic stem cell disease.

Singapore is the regional referral centre for hematopoietic stem cell transplants, which is a standard of care for complex blood cancers. Slow recovery of blood counts after transplantation gives rise to complications, increased medical bills and treatment failures.

We have participated in international clinical trials on blood stem cell expansion which have shown good efficacy in accelerating blood cell count recovery after transplantation, resulting in fewer infections and shorter hospitalisation.

Our team at Singapore General Hospital (SGH) has also embarked on a new clinical trial on cord blood stem cell expansion using novel technology developed by SGH, Duke-NUS Medical School, the National University of Singapore and the National Cancer Centre Singapore. Success in this

trial would mean that patients could undergo cord blood stem cell transplants with significantly reduced complications.



WOUND REGENERATION FOR TREATMENT OF SEVERE BURNS

According to the World Health Organization, burns are a global public health problem, accounting for an estimated 180,000 deaths annually.

Non-fatal burns are a leading cause of morbidity vis-a-vis prolonged hospitalisation, disfigurement and disability, often leading to stigma and rejection. It was estimated in 2004 that nearly 11 million people worldwide were burned severely enough to require medical attention.

Methods for treating severe burns have changed in recent decades, and an increasingly aggressive surgical approach with early excision and wound closure is advocated to reduce infection and improve mortality. Surgeons now face the challenge of excising and grafting larger burns of more than 50% of the total body surface area with limited skin availability.

Thus, it is imperative to find skin substitutes to supplement conventional split-thickness skin autografting. While cadaveric skin allografting provides wound coverage, it is temporary owing to tissue rejection after two to three weeks. In addition, there are limited supplies of skin allografts harvested from deceased donors.

Cultured skin, which is the expansion of autologous epithelial cells and their progenitors isolated from a small skin biopsy, is a potential solution for obtaining large amounts of epithelial cell sheets to treat extensive burns.

At the SGH Skin Culture Lab, we are harnessing the inductive properties of extracellular matrix to optimise epidermal stem cell growth. This is accomplished in a safe and well-defined micro-environment that complies with the standards of Good Manufacturing Practice.

We are also studying non-native sources of immunoprivileged epithelial cells, such as the umbilical cord lining for skin tissue engineering applications.

CONCLUSION

Important discoveries have helped to improve our understanding of how organs and tissues degenerate. This could lead to the development of new tools, diagnostics and therapies for organ and tissue regeneration. Patients will have a lot to look forward to with regenerative medicine due to exciting new developments in science, infrastructure, developmental tools and clinical trials.



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He is also an Executive Board Member of the Asia Pacific Blood and Marrow Transplantation Group, as well as a Board Organising Committee member of the Singapore Translational Cancer Consortium and Advanced Cell Therapy Research Institute of Singapore (ACTRIS).



Prof Jodhbir Mehta

*Deputy Head, SingHealth Duke-NUS Cell Therapy Centre;
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Professor Jodhbir Mehta is a distinguished Professor in Clinical Innovation in Ophthalmology at the Singapore National Eye Centre and the Deputy Executive Director, Head Tissue Engineering and Cell Therapy Group at the Singapore Eye Research Institute. His clinical work is focused on corneal transplantation, anterior segment reconstruction and refractive surgery.

He has won 52 awards internationally for clinical and research work, most recently the American Academy of Ophthalmology Senior Achievement Award 2017, Doug Coster Lecture from the Australian Corneal Society 2018, Charles Tillett Lecture 2020 and Casebeer Award 2020.



Prof Karl Tryggvason

*Lead (Cardiovascular),
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Professor Karl Tryggvason is a Professor at Duke-NUS Medical School, Singapore, Adjunct Professor at Duke University, North Carolina and Emeritus Professor at the Karolinska Institute, Stockholm.

His research concerns the molecular composition, biology and diseases of basement membranes (BM), a special compartment of the extracellular matrix. His group has cloned almost all human BM proteins and clarified genetic causes of many BM-associated diseases, such as Alport and congenital nephrotic syndromes, junctional epidermolysis bullosa and congenital muscular dystrophy.



Prof Teh Bin Tean

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Professor Teh Bin Tean is the Co-Director of the SingHealth Duke-NUS Regenerative Medicine Institute of Singapore, Deputy Medical Director (Research) at the National Cancer Centre Singapore and Principal Investigator of the Laboratory of Skeletal Muscle Regeneration.



Clin Prof Tan Bien Keem

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He is also the Regulatory & Compliance Lead for the SingHealth Duke-NUS Cell Therapy Centre as well as Assistant Director of the Transplant Tissue Centre at the SingHealth Duke-NUS Transplant Centre, where he is responsible for the regulatory compliance, operations, quality assurance and research of tissue transplantations for skin, cardiovascular tissues and iliac vessels.



GPs can contact the **SingHealth Duke-NUS Cell Therapy Centre** at sd.cell.therapy@singhealth.com.sg to know more about the available cell therapies and clinical trials on the SingHealth campus, or scan the QR code for more information.



Combating Sarcopenia – An Increasing Public Health Problem

Prof Teh Bin Tean

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Even as the prevalence of sarcopenia rises with Singapore's ageing population, current therapeutics options are suboptimal in effectively treating the condition. At the SingHealth Duke-NUS Regenerative Medicine Institute of Singapore, a different approach based on regenerative medicine is underway with the aim that an individual's unique clinical, molecular and lifestyle data will be key to combating the condition.

INTRODUCTION

Sarcopenia is one of the most prevalent health problems among the elderly in the ageing population of Singapore, which will put unprecedented pressure on our healthcare system.

First introduced by Irwin Rosenberg in 1989 as the **age-related loss of muscle mass**, it has recently been recognised as a disease state that has its own ICD-10 (International Classification of Diseases, Tenth Revision) code in 2016. This age-related process of quantitative and qualitative muscle loss is now considered **the precursory process of clinical frailty**.

Clinical frailty is not only associated with a poorer quality of life (QOL), but also increased hospitalisation and increased risk of surgical morbidity and mortality.

Prevalence in Singapore

Two recent epidemiological studies in Singapore, the Yishun Study and GERI-LABS 2 study, found that the prevalence of sarcopenia in the local community is between 27.0-32.2%.

In addition, those with sarcopenia were unsurprisingly associated with increased age, frailty and type 2 diabetes mellitus.

Diagnostic assessment

The Asian Working Group for Sarcopenia (AWGS) and European Working Group on Sarcopenia in Older People (EWGSOP) have both acknowledged the clinical significance and impact of sarcopenia in age-related and disease-related degeneration leading to frailty.

In 2019, both societies refined their research-oriented assessment and termed it as the Clinical Research Diagnostic Algorithm for Sarcopenia. It utilises a combination of objective measurements of appendicular skeletal muscle mass, muscle strength and physical performance.

For screening in the community, AWGS has recommended the inclusion of a simple measurement of calf circumference (for ambulant individuals) into their algorithm, improving the ease of sarcopenia screening.

Skeletal muscle has one of the most complex structures and intricate organisations, constituting approximately 40% of body mass. Not only does the muscle contract to enable locomotion, but it also modulates a plethora of biological networks that are essential to maintain human health.

Hence, any form of muscular disorder severely affects the QOL of patients as it compromises muscle architecture and contractile performance.

CURRENT TREATMENTS AVAILABLE

Unfortunately, there is a dearth of effective therapeutics available for muscle diseases, with exercise and nutritional interventions remaining the cornerstone of treatment.

This can be largely attributed to the frustrating series of failed clinical trials that pharmacologically target specific pathways to eradicate muscle diseases. Most of these drugs could neither translate into a significant increase in muscle size nor elicit any functional improvement.

1 Pharmacological treatments

To date, commonly prescribed drugs to treat certain muscle diseases include a **combination of growth hormone and testosterone**.

Limitations

However, there is mounting evidence that these therapies elicit marginal beneficial outcomes with minimal changes in body composition and strength. In addition, these treatments have considerable side effects, limiting application in clinical practice.

Despite the setbacks, there are still massive efforts to develop pharmacological drugs to treat skeletal muscle atrophy due to the vested interest from pharmaceutical companies, as muscle remains an undermedicated organ.

The drug development pipeline for muscle diseases includes myostatin/activin receptor type IIB signalling inhibitors, muscle troponin complex activators, exercise mimetics and anabolic stimulants.

2 Nutritional interventions

One underlying cause of muscle wasting can be attributed to malnutrition or nutrient deficiencies such as in vitamin D or B12. Malnutrition is a key pathophysiological driver of sarcopenia, exacerbating muscle wasting in elderly patients.

Recommendation

The International Conference of Frailty and Sarcopenia Research (ICFSR) International Clinical Practice Guidelines for Sarcopenia recommend that clinicians consider **protein supplementation or a protein-rich diet** for treatment of sarcopenia in older adults.

Several studies have demonstrated that branched-chain amino acids, whey protein, leucine and its metabolite β -hydroxy β -methylbutyrate (HMB) can improve muscle mass and strength in specific clinical populations and in sarcopenic patients. Even though the principal findings of these studies have garnered traction among clinicians, the quality of evidence is still subpar, warranting further investigation with higher quality study design.

Other promising nutritional interventions that can potentially attenuate muscle loss in clinical populations include fish oil-derived, long-chain omega-3 polyunsaturated fatty acids and multivitamin/multimineral supplements.

3 Exercise prescription

Different modalities of exercise remain the foundation for improving cardiovascular fitness, inducing muscle hypertrophy and increasing strength in patients with sarcopenia. Mechanistically, both aerobic and resistance exercises have been shown to induce mitochondria biogenesis, ATP production and protein synthesis, and to suppress catabolic networks.

The COVID-19 pandemic, in which physical activity is restricted thus promoting sedentary behaviour, can further result in the loss of muscle mass and function in geriatric patients.

Recommendation

ICFSR recommends that seniors participate in a **progressive physical activity programme** which encompasses a **resistance training** element.

Limitations

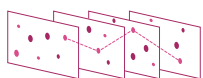
Clinically, there is no consensus on an effective exercise prescription, and it is incumbent on healthcare professionals to formulate individualised intervention to optimise treatment outcomes.

In addition, patients with underlying health conditions may lack intrinsic motivation to adhere to the strict physical programme, rendering the need to pivot towards an alternate therapy that is suboptimal.

Finding a Cure Beyond the Current Therapeutics

Overall, pharmacological options have shown minimal benefits and considerable side effects, with many clinical trials yielding poor outcomes.

Thus, the **SingHealth Duke-NUS Regenerative Medicine Institute of Singapore (REMEDI^S)** aims to rejuvenate the field through a comprehensive approach to muscle research and stem cell therapy development. By building an increased knowledge of sarcopenia, REMEDI^S aims to drive the discovery of more effective biomarkers and better interventions.



MULTI-OMIC APPROACH TO FURTHER UNDERSTAND SARCOPENIA

Due to the limitations of current treatments, it may be critical to rethink our strategy in developing innovative therapeutics strategies by first **galvanising the field of muscle research**.

A radical shift in research direction is warranted, and our laboratory has taken a comprehensive, multipronged approach to study muscle diseases, which is often systemic and multifarious in nature.

To date, we have established a muscle-specific repository to address the need for sarcopenia research, which we believe is the first of its kind in Singapore.

The strategy will be to perform multi-omic profiling of these muscle materials in an effort to unravel the regulatory and signalling networks involved in the pathogenesis of sarcopenia.

Interrogating epigenetic factors, for example, can potentially open a new avenue for drug discovery and therapeutics, as several bodies of evidence suggest that epigenetic changes are a major contributor to the development of sarcopenia.

We aim to discover novel biomarkers for relevant cohorts by further leveraging on this biorepository of sarcopenia-specific biomaterials including serum.

A combination of tissular and serum biomarkers in tandem with anthropomorphic and imaging measurements will address an unmet clinical need that will greatly improve the prediction, diagnosis, prevention and management of sarcopenia.

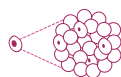


DEVELOPING STEM-CELL-BASED THERAPIES

Another research goal of ours is to develop stem-cell-based therapies that have long been heralded as a promising means to treat incurable diseases since the discovery of induced pluripotent stem cells (iPSCs), which led to a paradigm shift in the field of regenerative medicine.

However, optimism has since dwindled as the effectiveness and success of iPSCs are still under intense scrutiny. This is especially apparent when attempting to generate myogenic cells from stem cells, whereby a multitude of limitations impede the progress towards utilisation in clinical trials for muscle repair.

To date, our team has established a scalable serum-free platform for the directed differentiation of human PSCs into a homogenous population of myotubes, eliminating the need for transgene overexpression.



BIOENGINEERING 3D MYOFIBER ORGANIDS

To further recapitulate key phenotypic and functional aspects of human skeletal muscle, our team has demonstrated the ability to bioengineer **3D myofiber organoids that manifest mature contractile apparatus**.

Using this platform, we are able to model the human features of a chronic metabolic disease, and identify both its pathogenic mechanism and therapeutic targets. To highlight the potential to translate these findings into clinical settings, these muscle organoids have been successfully engrafted in preclinical models.

CONCLUSION

The translation of findings from laboratory benches to the patients' bedside is often challenging. However, elucidating the mechanistic underpinnings of sarcopenia will improve clinicians' understanding of the multiorgan, multifactorial process of age-related muscle loss. In doing so, synergistic collaboration between clinicians and basic scientists can lead to the discovery of more effective diagnostic and prognostic biomarkers.

Increased knowledge of sarcopenia and its management will improve interventions that can be tailor-made to different stages of sarcopenia – a step towards precision medicine. It is conceivable that a multimodal, multidisciplinary approach based on an individual's unique clinical, molecular and lifestyle data will be key to combating this increasing health problem in our ageing population.



Prof Teh Bin Tean

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Professor Teh Bin Tean is the Co-Director of the SingHealth Duke-NUS Regenerative Medicine Institute of Singapore, Deputy Medical Director (Research) at the National Cancer Centre Singapore and Principal Investigator of the Laboratory of Skeletal Muscle Regeneration.



Asst Prof Koh Hong Xiang Frederick

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Assistant Professor Frederick Koh is an Associate Consultant in the Colorectal Service, Department of General Surgery, Sengkang General Hospital. His clinical interests include the various aspects of colorectal surgical oncology, proctology as well as acute care surgery.



Apart from clinical contributions, Prof Koh places emphasis on the importance of academic surgery. He is published in numerous peer-reviewed journals, and enjoys both clinical and basic science research pertaining to the fields of General and Colorectal Surgery. He has held grants and has experience in conducting both population-based and trial-based research, and intends to continue his pursuit of academia in order to continue participating in the continuous improvement of clinical practice to serve his patients best. He is currently pursuing a PhD with Duke-NUS around the theme of sarcopenia in surgical patients.



Dr Chua Min Wen Jason

Research Fellow, Division of Medical Sciences, National Cancer Centre Singapore

Dr Chua Min Wen Jason is a Research Fellow at the Division of Medical Sciences at the National Cancer Centre Singapore. His research interests focus on modulating stem cells into muscle organoid to model muscle disease and to unravel novel signalling networks driving the progression of sarcopenia. In addition, Jason is passionate about sustainable food-tech innovation, with a special interest in cultured meat research to address the issue of food security in land-scarce Singapore.



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Advancing Cartilage Regeneration Through Cellular Therapy for Chondral Defects of the Knee

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With ongoing advancements in cell-based therapies for cartilage repair, we can look forward to more accessible treatments and better patient outcomes for knee osteoarthritis and chondral defects of the knee. Find out more about the promising developments on the horizon and what they could mean for patients.

INTRODUCTION

The treatment of articular chondral defects of the knee has classically been challenging, due to the cartilage's aneural, avascular and alymphatic nature. This makes natural healing of chondral defects almost impossible.

CAUSES OF CHONDRAL DEFECTS OF THE KNEE

Patients can suffer from chondral defects from two main knee conditions: knee osteoarthritis and acute focal chondral injury.



1 Knee osteoarthritis

Age

This generally occurs in the older age group of patients 45 years and above.

Causes

Osteoarthritis is the gradual wear of the cartilage due to various factors such as:

- Biomechanical factors with malalignment being the most common
- Previous injury factors such as previous meniscus injuries which reduce shock absorption on the cartilage
- Inflammatory factors such as gout and rheumatoid arthritis

Presentation

The wear of the cartilage is generalised and chondral defects can occur from minor trauma, such as light jogging or twisting injuries, leading to a chondral flap tear and resultant defect when the tear detaches.

The defect side causes acute joint pain and swelling, and patients have pain on weightbearing and stair climbing.

2 Acute focal chondral injury

Age

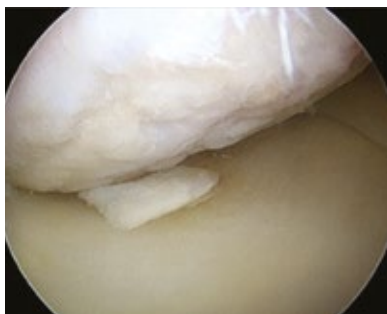
This generally occurs in the younger age group of patients from paediatric to 45 years.

Causes

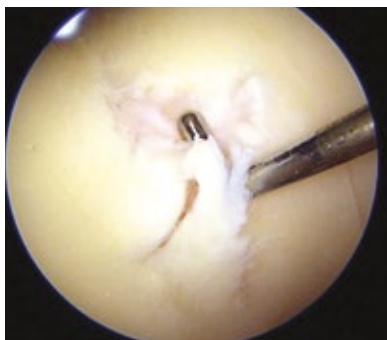
There is no generalised wear of the cartilage. Instead, a focal chondral defect is created due to an acute injury such as a sporting injury (e.g., anterior cruciate ligament tear via twisting injury, patella dislocation, landing from a jump of significant height).

Presentation

The chondral defect may be accompanied by bone loss, leading to an osteochondral defect. In addition to the symptoms of knee osteoarthritis, the detached fragment may be a loose body and might cause locking of the knee joint.



A Older patient group with osteoarthritis and a resultant detached chondral flap. Note the generalised wear of the cartilage.



B Younger patient group with traumatic injury to the cartilage with a chondral defect and cartilage flap.

Figure 1 Arthroscopic pictures of chondral injuries in two different groups of patients

CURRENT ROUTINE CARTILAGE REPAIR STRATEGIES AND THEIR LIMITATIONS

Cartilage regeneration strategies can be broadly divided into non-cell-based therapy versus cell-based therapy.

1 Non-cell-based therapy

The gold standard for non-cell-based therapy is that of **intrinsic repair enhancement**.

What it is

With the use of microfracture, the surgeon creates holes through the tidemark of the subchondral bone after debriding the nonviable cartilage. This allows for marrow stimulation which will form blood clots, which in turn will mature into fibrocartilage to fill up the defect.

Limitations

This, of course, is inferior to that of native articular cartilage.

2 Cell-based therapy

Cell-based therapies include the gold-standard **autologous chondrocyte implantation (ACI)**, a two-stage surgery.

What it is

In the first stage, the surgeon harvests healthy cartilage and sends it to the laboratory for culture. Thereafter, the cultured chondrocytes are embedded into a synthetic scaffold matrix. The cell-embedded matrix is then used for the second stage of surgery, where the chondral defect is debrided and the matrix is secured to the base of the debrided chondral defect via tissue glue.

Limitations

However, this method is costly, requires two surgeries, and is associated with donor site morbidity and has largely been avoided.¹

A LATEST SURGICAL OPTION: AUTOLOGOUS MATRIX- INDUCED CHONDROGENESIS

Apart from ACI, which is available in Singapore, surgeons are advocating for a surgical procedure that requires only one surgery with minimal donor site morbidity.

Autologous matrix-induced chondrogenesis (AMIC) has thus been popularised amongst surgeons for exactly that. This surgery involves the use of a synthetically-created scaffold that aids in the regeneration of cartilage with the help of marrow stimulation techniques such as microfracture or chondroplasty.

To improve the biological aspects of repair, many surgeons advocate for the use of bone marrow aspirate concentrate (BMAC) which contains bone marrow mesenchymal stem cells (BM-MSC) in small concentrations along with growth factors and cytokines.²

A single-step procedure

The surgeon would harvest BMAC from the iliac crest and spin it down to a concentrate. Thereafter, the BMAC will be embedded into the scaffold and then grafted to the debrided chondral defect as a one-stage surgery, avoiding the complications of ACI.

Results from randomised controlled trials have shown comparable results at two years between ACI and AMIC.³

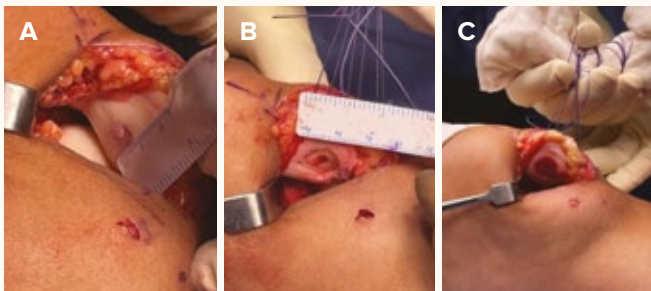


Figure 2 The surgical procedure of AMIC

- A.** Chondral defect of the patella
- B.** Debridement of the unhealthy cartilage to stable edges
- C.** AMIC and BMAC scaffold application

FUTURE POTENTIAL CELL-BASED THERAPIES FOR CARTILAGE REGENERATION

1 Autologous bone marrow mesenchymal stem cells (BM-MSC)

To circumvent the need for two surgeries and to improve the clinical outcomes of cartilage regeneration, the search for an alternative cell source has been ongoing for the last 10 years.

A suitable candidate to substitute ACI chondrocytes was autologous BM-MSC, which are **bone marrow stem cells harvested from the patient's own bone marrow**.

Benefits

Researchers in Singapore have shown that concentrated autologous BM-MSC in high dosages (without scaffold), at 10 years follow-up in clinical trials:⁴

- Was as effective
- Required one less surgery
- Was cheaper
- Has much lesser donor site morbidity

For AMIC with BMAC, the results were more successful for patients under 45 years old.

However, with concentrated BM-MSC alone, there were no significant differences seen for patients at any age, indicating superiority in the use of concentrated BM-MSC.⁴ We hope to see this option available in routine clinical practice soon.

BM-MSC has also been investigated as an intra-articular injection for chondral defects with good results, and this is a potentially attractive option as it can be administered in the clinics.⁵

2 Other sources of stem cells

Other sources of stem cells being investigated for cartilage regeneration include adipose-derived stem cells and umbilical cord blood-derived stem cells, and there are clinical trials using these stem cells for intra-articular injections for osteoarthritis of the knee.

There has been evidence of improving pain and function of the knee in the short term, but the evidence is still limited in terms of actual cartilage regeneration and long-term results.⁶

3 Further in the future: 'Cell-free' cartilage regenerative therapy – stem cell exosomes

Limitations of autologous stem cells

Cell-based therapies such as autologous BM-MSC may have promising results, but autologous stem cells have limited cellular capacity for self-renewal, proliferation and differentiation with increasing donor age.

Cell-based therapies thus pose significant logistic and operational challenges associated with proper handling and cell storage to maintain cell viability and vitality.

Paradigm shift in understanding MSC therapy

There is increasing evidence that MSC therapy is not dependent on the engraftment of cells at the site of injury, followed by differentiation of the MSC to the target cell type.⁷

We used to believe that the stem cells, when injected to the injury site, will attach to the injury site and then differentiate into the target cell type to regenerate new tissue. However, this is not the case.

There has been a paradigm shift with evidence that MSC are signaling cells, or 'messenger signaling cells', that mediate the effect by secretion of trophic factors. These trophic factors then stimulate the intrinsic repair of the damaged tissues.

MSC exomes as 'cell-free' therapy

One of these important factors is the MSC exosome. MSC exosomes are nano-sized, cell-secreted bi-lipid membrane vesicles of about 40-100 nm present in the MSC secretome that have been found to possess potent immunomodulatory and regenerative properties.⁷

Animal studies have been performed and MSC exosomes alone without scaffold have demonstrated significant cartilage regeneration of articular hyaline cartilage, similar to native cartilage, with comparable histological and biomechanical properties.⁸

This 'cell-free' regenerative therapy, which is a clear liquid that can be commercialised and injected in clinics, is an exciting field to watch for the future of bringing cartilage regeneration into clinics.⁸

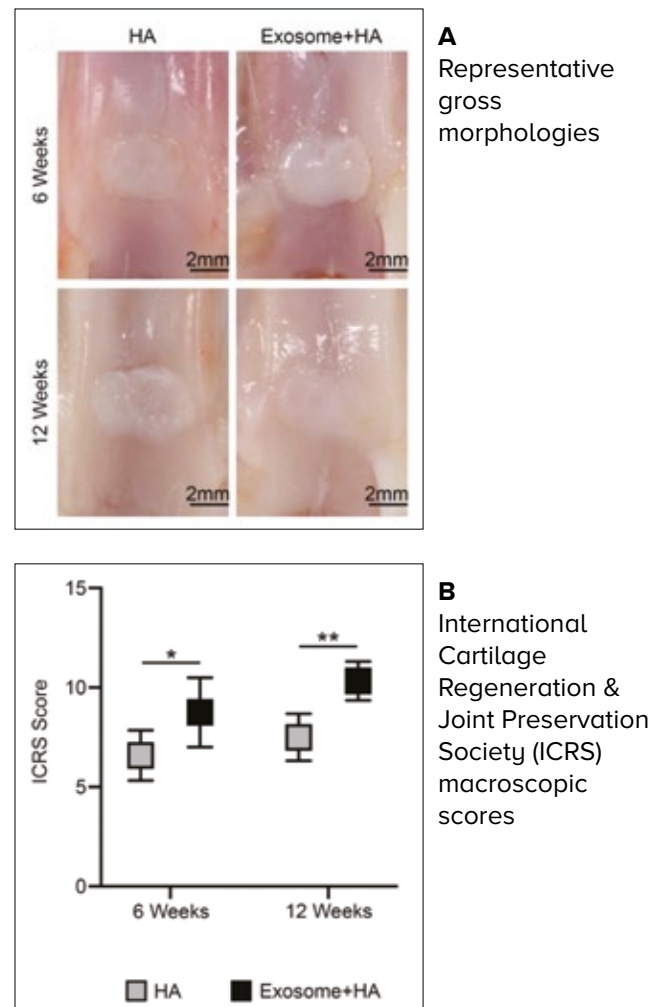


Figure 3 Animal studies showing superior cartilage regeneration with MSC exosomes and hyaluronic acid (HA), as compared to HA alone.⁸

Values represent the means \pm 95% CI.
* $P < 0.05$, ** $P < 0.01$ compared to HA group.
Scale bar: 2 mm.

CONCLUSION

Current cell-based therapies for cartilage regeneration involve the usage of AMIC and BMAC, but have less successful outcomes in patients above 45 years old. More advanced cellular therapy options for cartilage regeneration, such as concentrated forms of BM-MSc, have shown sufficient clinical evidence for future routine clinical practice and may be suitable for older patients above 45 years old.

The future of cartilage regeneration is exciting and may venture into cell-free therapy that can be delivered to the clinics, such as that of MSC exosomes.

REFERENCES

1. Mistry H, Connock M, Pink J, Shyangdan D, Clar C, Royle P, Court R, Biant LC, Metcalfe A, Waugh N. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. *Health Technol Assess*. 2017 Feb;21(6):1-294. doi: 10.3310/hta21060. PMID: 28244303; PMCID: PMC5346885.
2. Gobbi A, Whyte GP. Long-term Clinical Outcomes of One-Stage Cartilage Repair in the Knee With Hyaluronic Acid-Based Scaffold Embedded With Mesenchymal Stem Cells Sourced From Bone Marrow Aspirate Concentrate. *Am J Sports Med*. 2019 Jun;47(7):1621-1628. doi: 10.1177/0363546519845362. Epub 2019 May 16. PMID: 31095402.
3. Fossum V, Hansen AK, Wilsgaard T, Knutsen G. Collagen-Covered Autologous Chondrocyte Implantation Versus Autologous Matrix-Induced Chondrogenesis: A Randomized Trial Comparing 2 Methods for Repair of Cartilage Defects of the Knee. *Orthop J Sports Med*. 2019 Sep 17;7(9):2325967119868212. doi: 10.1177/2325967119868212. PMID: 31555714; PMCID: PMC6749791.
4. Teo AQA, Wong KL, Shen L, Lim JY, Toh WS, Lee EH, Hui JHP. Equivalent 10-Year Outcomes After Implantation of Autologous Bone Marrow-Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation for Chondral Defects of the Knee. *Am J Sports Med*. 2019 Oct;47(12):2881-2887. doi: 10.1177/0363546519867933. Epub 2019 Aug 21. PMID: 31433674.
5. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. *Arthroscopy*. 2013 Dec;29(12):2020-8. doi: 10.1016/j.arthro.2013.09.074. PMID: 24286801.

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His clinical interests are in sports medicine and sports surgery, in particular cartilage regeneration and restoration, where he became the first Fellow of the International Cartilage Regeneration & Joint Preservation Society from South-East Asia.

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From Clinical Trials to Bedside Signature Collaboration Addresses Growing Demand for Cell Therapeutics in Singapore

Find out how the partnership between the SingHealth Duke-NUS Cell Therapy Centre and the Advanced Cell Therapy and Research Institute, Singapore enables the delivery of quality cell therapy products for the benefit of patients.

ABOUT CELL THERAPY

Cellular therapy involves the introduction of whole cells into a patient to carry out an immunotherapeutic or regenerative function to treat diseases and/or damaged organs. Cell therapy, as witnessed by the regulatory approval of several life-saving products, will be a rapidly evolving and developing field in the medical ecosystem for years to come.

From Discovery to Manufacturing The Advanced Cell Therapy and Research Institute, Singapore



The Advanced Cell Therapy and Research Institute, Singapore (ACTRIS) was set up to address the growing demand for cell therapy in Singapore. Established in April 2020, ACTRIS is a business unit of the Consortium for Clinical Research and Innovation, Singapore (CRIS), which oversees national translational and clinical research programmes under the stewardship of the Ministry of Health (MOH).

ACTRIS' vision is to be the national and regional centre of excellence for **facilitating the discovery, process development and manufacturing of cellular-based therapeutics** across the broad spectrum of immunotherapy and regenerative medicine encompassing investigational and approved cell therapies (CTs).

The team seeks to promote and foster the entire value chain of the CT ecosystem through enabling:

- Translational research and development
- Manufacturing
- Clinical application
- Commercialisation

Its planning, management and operational teams are led by Dr Tan Lip Kun, a Haematologist from the National University Health System. Supported by MOH, Dr Tan and the implementation office team bring together years of clinical, laboratory and administrative experience that is quintessential in building a national-level programme.

ACTRIS' new facility will be located in the new National Cancer Centre Singapore building at the Singapore General Hospital (SGH) campus by 2022.

To find out more about ACTRIS, visit www.actris.sg.

HOW ACTRIS ENABLES THE ADVANCEMENT OF CELL THERAPY

International accreditation

Located on the SGH campus, the centralised ACTRIS facility will attain accreditation from national and international regulators to ensure quality and compliant CT product development and services.

Through the availability of Current Good Manufacturing Practice (cGMP) and Global Trader Programme (GTP) laboratories, ACTRIS will serve the public healthcare, academic and private sectors operating on a translational, academic and commercial business model.

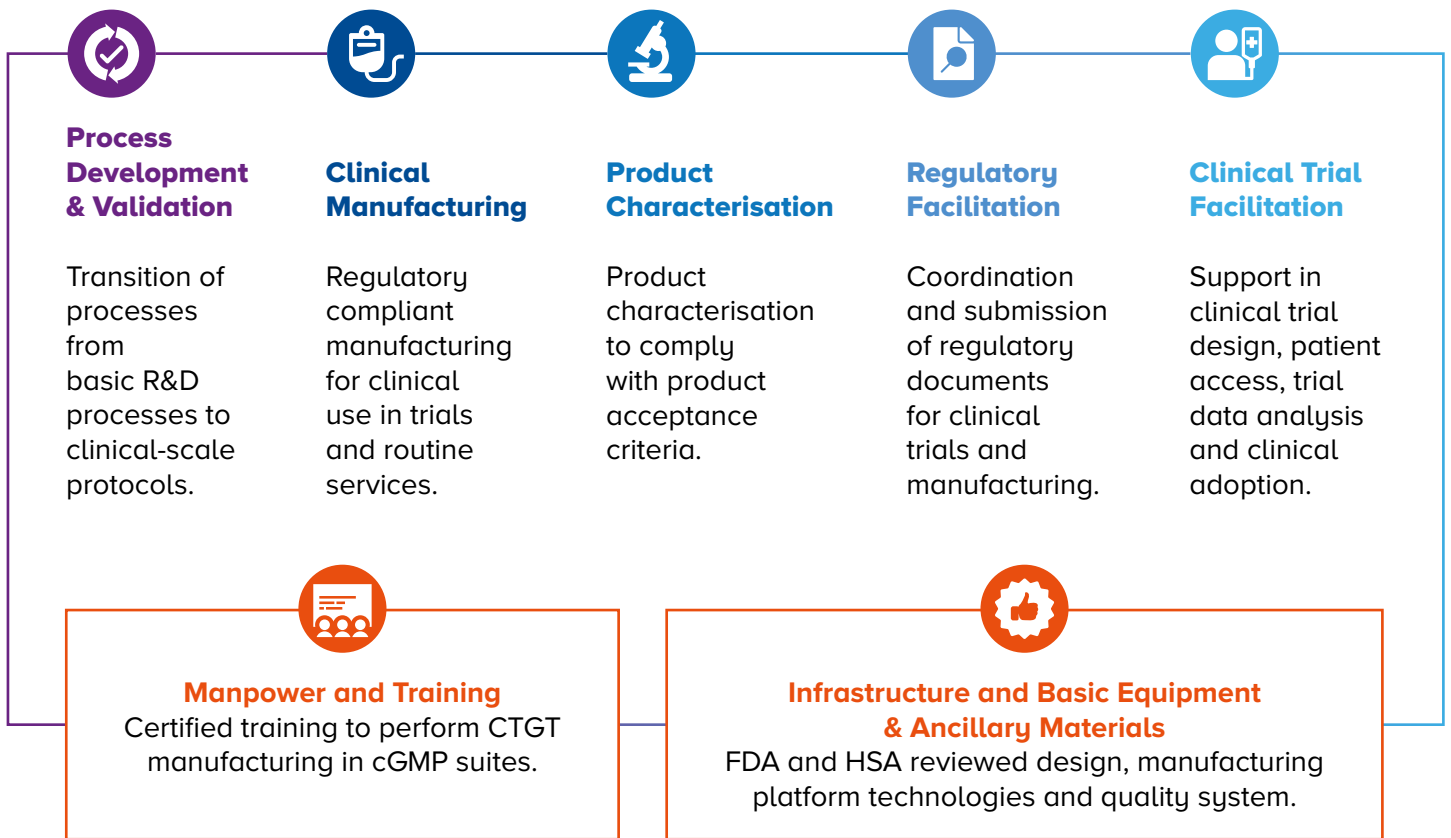
Value-added services

To enable the growth of Singapore as an innovation-led biomedical hub particularly in the niche domain of CTs, ACTRIS will also provide value-added services such as workforce training, business strategy, regulatory facilitation and health economics pertaining to the delivery of CT to patients compounded with necessary economic value capture.

Manufacturing services

Through the formation and operationalisation of ACTRIS, it hopes to deliver manufacturing services to bring affordable cell, tissue and gene therapy (CTGT) products to patients in Singapore.

END-TO-END CLINICAL PROCESS DEVELOPMENT AND MANUFACTURING CAPABILITIES



PARTNERSHIP BETWEEN ACTRIS AND THE SINGHEALTH DUKE-NUS CELL THERAPY CENTRE (SDCT)

A key mandate of SDCT is to run clinical trials and services for cellular therapeutics. The strategic partnership between SDCT and ACTRIS will ensure smooth clinical manufacturing services to provide quality-controlled cellular therapy products to patients.

As the field of CT continues grow in Singapore, we can expect the healthcare industry to evolve along with it. In the near future, general practitioners and community hospitals will play a pivotal role in looking after the well-being of patients who were successfully treated with cellular therapy products, as they become more accessible.

Driving Integrated and Transformative Care with Cell Therapy

The SingHealth Duke-NUS Cell Therapy Centre



IMPROVING CLINICAL CARE AND PATIENT OUTCOMES

The **SingHealth Duke-NUS Cell Therapy Centre (SDCT)** was launched in May 2021 to provide a cluster-wide focal point in coordinating **cell, tissue and gene therapy (CTGT)** research and education, as well as clinical trials and services.

This integrated and virtual centre brings together the strengths and expertise of healthcare professionals across various specialties in SingHealth institutions, to leverage on advanced CTGT technologies to improve diagnostics, therapeutics, research and healthcare outcomes by providing seamless, holistic and quality patient-centric care.

SDCT aims to be a global leader in delivering CTGT products and technologies, with a vision to make cellular immunotherapy available to Singapore and the Asia-Pacific region.

RESEARCH & EDUCATION

Research

Besides enhancing patient care, SDCT also focuses on formulating and coordinating cluster-wide efforts in the research and development of novel CTGT products and associated technologies.

Education

Additionally, the Centre organises educational programmes such as the monthly Cell Therapy

Lecture Series, bimonthly External Speaker Seminar Series and annual Cell Therapy Conference to equip medical professionals with knowledge of the use of cellular therapies in clinical trials and services.

SDCT will be organising more educational programmes in the near future.

Below are some programmes that may be relevant to general practitioners (GPs):

- 1. GP forum:** To educate GPs on the landscape of cell therapy in cancer and regenerative medicine, and the myths and truths of cell therapy.
- 2. Public forum:** To promote awareness of CTGT clinical services, including the institutions that provide such services, and to provide up-to-date information to patients and families.
- 3. Multidisciplinary forum:** To educate Accident & Emergency, palliative and supportive care teams (e.g., social workers) on complications related to cell therapies, to improve patient outcomes and keep clinical partners updated and involved in these outcomes.
- 4. Patient support group:** To provide a platform for cell therapy patients to share their journey with others and receive emotional and moral support.

GPs who would like to know more about SDCT's educational programmes, or join the mailing list to be updated on SDCT's news, events and activities, please email to sd.cell.therapy@singhealth.com.sg.

COLLABORATIVE PARTNERSHIPS

The Centre works with the Advanced Cell Therapy Research Institute, Singapore (ACTRIS) and the Regenerative Medicine Institute of Singapore (REMEDI), and closely coordinates efforts with other national and international stakeholders to establish Singapore as the regional hub of CTGT.

Our Services & Capabilities

Cell Therapy Administration

- Personalised and holistic care experience for patients undertaking cell therapy
- Patient support groups, in collaboration with pharmaceutical companies, for patients to share their journey with others and receive emotional and moral support

Research & Development

- Development of cell-therapy-related studies from pre-clinical to clinical study execution

- Expertise in regulatory aspects and operations pertaining to cell therapies
- Close relationship with ACTRIS' Good Manufacturing Practice (GMP) team to help with Chemistry, Manufacturing, and Control (CMC) requirements and process development in related studies
- FACT-JACIE-accredited Apheresis Collection Facility on-site

GPs who would like to find out more, please contact the SingHealth Duke-NUS Cell Therapy Centre:

Email: sd.cell.therapy@singhealth.com.sg

Website: www.singhealth.com.sg/cell-therapy-centre

Our Executive Committee

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Dept of Haematology, SGH

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Dept of Cornea & External Eye Disease, SNEC

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