The ACTO Times

Asian Cellular Therapy Organization

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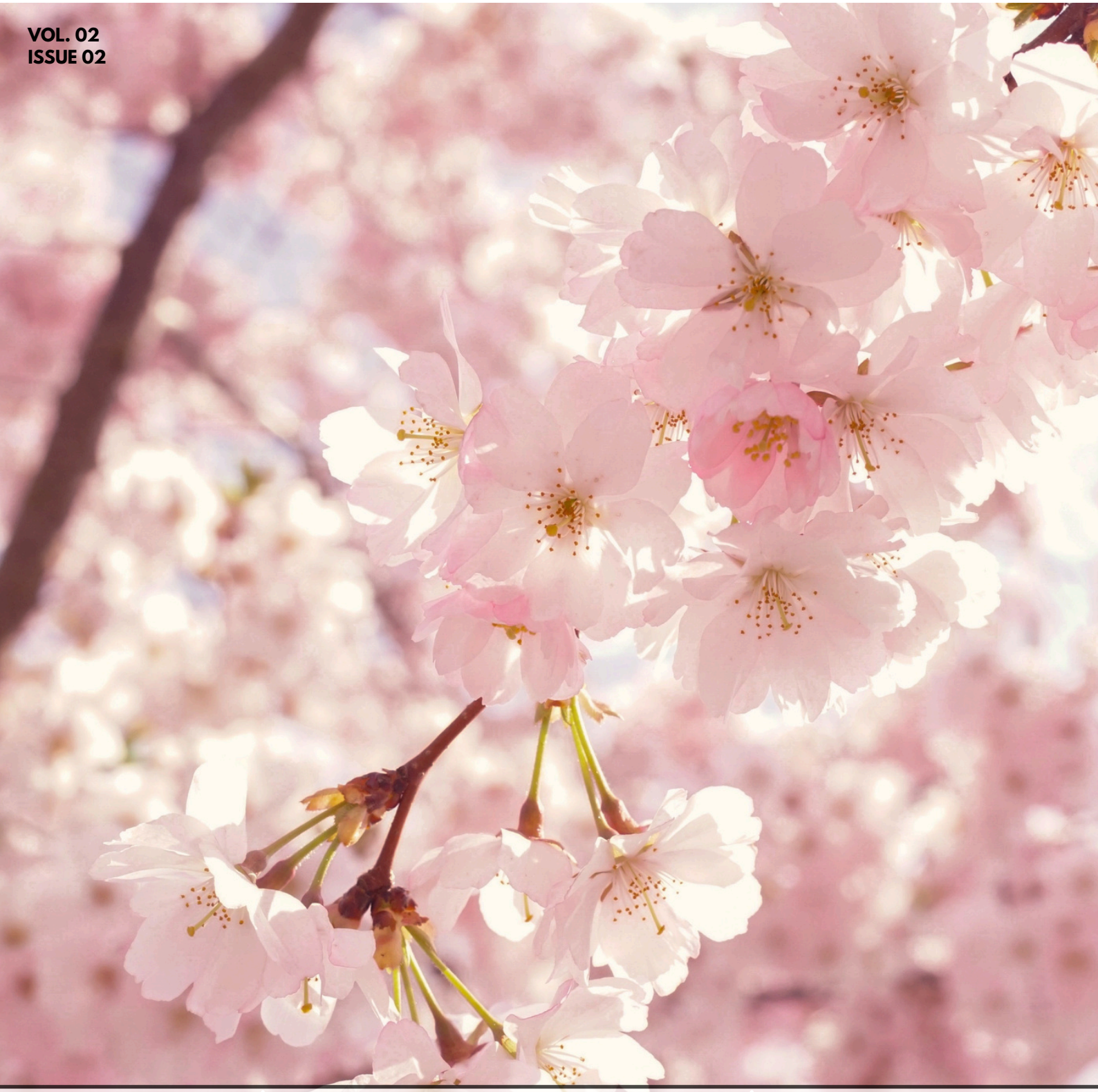
ISSUE 02



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2025 SPRING EDITION

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Asian Cellular Therapy Organization
2025 SPRING EDITION

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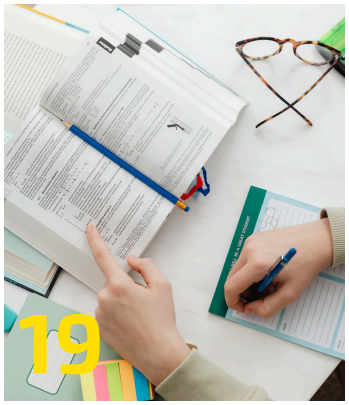

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Greetings
The ACTO Chairperson

Dear ACTO members,

It is our great pleasure to distribute the second issue of ACTO Times 2025.
We are facing unstable situation globally today. We do respect freedom and pursue benefit of each country. However, freedom and benefit of own country can be respected only when those country also equally respect other country's freedom and benefit. I hope this uncertain situation will be settled soon in reasonable manner. We need a country of virtue. We lost the leading country of virtue and facing those selfish countries today.

Regarding the new technology development today, exosome became a hot topic among us. However, there are issues regarding the control of exosome clinical development. There is no specific regulation which directly control exosome yet. Any materials administered in human being must have safety data and some information suggesting expected efficacy. All clinical study, any clinical procedure/material, should start as clinical study until its safety and efficacy is confirmed. Then the clinical procedure/material can be used as routine therapy.
Any trials must follow current regulation, even existing regulation is not directly covering the material/molecule, gold standard, there should be safety data and efficacy suggesting information. Then its study must be approved by ethics committee and study protocol must be applied to regulatory agency. Then outcome of the study must be published. If everyone follows this principal, there will be no issues. Our duty is to follow ethical standard and regulations and to share correct information with others. Publish negative data is also important for those others who may have similar idea. Confirm negative data is difficult because there may be error in your study. Publish confirmed negative data is more difficult than publishing positive data. We need to have the way to publish negative data.
Among us, regenerative therapy using cells/organ is important field for us in the field of cell and gene therapy.
ACTO will serve for those in the filed of cell and gene therapy in academy, industry and regulatory agency for the benefit of patient and their family.

Chairperson, Asian Cellular Therapy Organization (ACTO)
Akihiro Shimosaka

Akihiro Shimosaka

Editor's Column
The ACTO Times Editor-in Chief

Dear Readers of The ACTO Times,

I am thrilled to present the 2025 Spring Edition, highlighting the recent advances in Asian cell and gene therapy (CGT) at the start of this year.

In 2025, significant progress is being made in oncology and gene therapy. There are now over 100 CGT products available globally, with a particular focus on allogeneic and gene-editing products. The US FDA and EMA continue to lead in CGT product approvals, while Asia is experiencing rapid growth, particularly in the CGT market and clinical trials.

3D organoid platforms are emerging as a popular alternative to animal studies. The US FDA and EMA are currently developing guidelines for the use of 3D organoids in drug development. In Asia, Japan and Korea are making notable strides. Japan is actively involved in the research and development of 3D organoids, while Korea has implemented the Act on Advanced Regenerative Medicine and Advanced Biological Products (ARMAB) in February 2025 to support 3D organoids and other advanced regenerative medicine technologies.

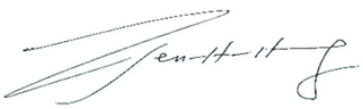
Additionally, there are exciting developments in the field of extracellular vesicles (EVs) and their clinical trials. So far, no EV product has been approved. In alignment with MISEV2014, 2018, and 2023, the regulations regarding the pharmacokinetics/pharmacodynamics (PK/PD) and mechanism of action (MOA) for EV therapy are still under discussion.

Finally, we are excited to announce that the 2025 ACTO annual meeting will be held in Singapore. This event will bring together experts and leaders in the field to discuss the latest advancements and future directions in cell and gene therapy. We warmly invite you to join us.

We hope you enjoy this edition and look forward to your continued support.

Sincerely,

Rita YH Huang, Distinguished Professor
Editor-in-Chief The ACTO Times
ACTO, Asian Cellular Therapy Organization



Rita YH Huang

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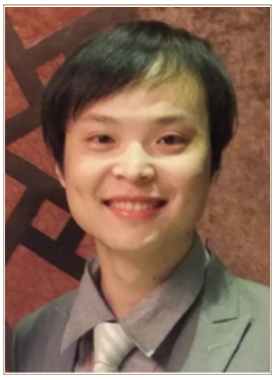

Yung-Che Kuo, PhD
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Kuo is an Assistant Research Fellow, TMU Research Center of Cell Therapy and Regeneration Medicine member and TMU Research Center of Thoracic Medicine. He is also a Director of Core Laboratory of Good Tissue Practice (GTP), Taipei Medical University, Taipei, Taiwan.

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Reno is a PhD Student in Taipei Medical University. He is also a faculty member of Medicine & Health Sciences in Universitas Muhammadiyah Jakarta. His interest focuses on molecular medicine and molecular oncology.

Karen Kitchley, M.Sc
Madurai

Karen is a PhD student at the Taipei Medical University. Her research focuses on exosomal therapy on hepatocellular carcinoma and exploring their mechanism of action.

Tony Yu-Xiu Lin, MS
Taipei

Tony is a PhD student at the Graduate Institute of Pharmacology, National Taiwan University College of Medicine. His research focuses on MSC culture and therapy, specifically exploring their role in regenerative medicine.

UNVEILING THE TIMELESS TAPESTRY

THE CHRONICLE OF ACTO THROUGH TIME

ACTO, the Asian Cellular Therapy Organization, serves as a dedicated platform for fostering the growth and progress of cellular therapy in the Asian context. It aims to respond more dynamically to the specific challenges and opportunities found in the diverse healthcare and research landscape across Asia.

ACTO is dedicated to driving advancements in cell and gene therapy (CGT), including research, clinical applications, industry collaborations, and global regulation. It seeks to facilitate collaborative environment where professionals, researchers, industry leaders, and regulatory agencies can come together to share knowledge, experiences, and innovations in CGT.

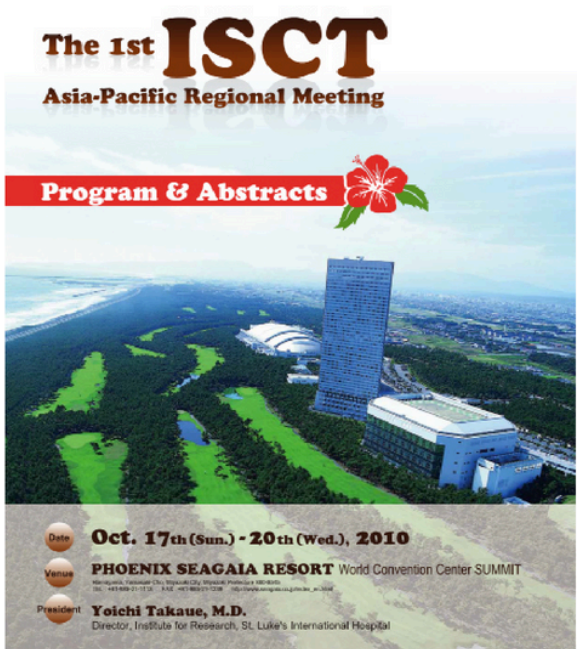
By doing so, ACTO envisions creating a comprehensive ecosystem that accelerates the translation of CGT research into practical applications, benefiting patients and contributing to the broader field of regenerative medicine. Through its activities, publications, and events, ACTO aims to play a crucial role in shaping the future of cellular therapy in Asia and contributing to the global discourse on regenerative medicine.

Since its establishment stemming from the ISCT Asian Regional Meeting, ACTO has evolved into a dynamic organization with a broad presence covering 15 regional territories, including Bangladesh, China, India, Indonesia, Iran, Japan, Jordan, Israel, Korea, Malaysia, Taiwan, Thailand, Singapore, Vietnam, and Pakistan. The expansion of ACTO into these territories not only amplifies the impact of CGT initiatives but also facilitates the exchange of knowledge and expertise across borders.

This collaborative approach aligns with ACTO's overarching mission to create a vibrant and interconnected network dedicated to advancing CGT within the diverse landscape of Asia.

The inclusion of these 15 regional territories served by ACTO highlights the varied landscapes, healthcare systems, and research environments across Asia. It demonstrates ACTO's recognition of the importance of tailoring CGT initiatives to the unique needs, challenges, and opportunities specific to each region.

Looking ahead, the ACTO organization remains committed to its regional focus, striving to further expand its presence and influence to better serve the diverse needs of the Asian CGT community.



PRELUDE

NAVIGATING THE UNIQUE DYNAMICS OF CGT IN ASIA

In the vibrant landscape of CGT. "The ACTO Times" unfolds as a chronicle attuned to the distinctive characteristics that define the Asian population. This prelude invites readers into a realm where the convergence of a large and diverse populace, intricate gene backgrounds, evolving regulations, and culture-related intricacies shape the narrative of CGT in Asia.

Large Population Dynamics

Asia, with its colossal and diverse population, charts a path for CGT that is both unprecedented and dynamic. "The ACTO Times" embarks on a journey to unravel how the sheer scale of population diversity influences research, clinical applications, and the industrial landscape of CGT.

Gene Background Diversity

Within the mosaic of Asian societies lie rich variations in gene backgrounds. This prelude delves into the intricacies of genetic diversity, exploring how the tapestry of genes across Asian populations influences the trajectory of CGT, from personalized medicine to targeted therapies.

Culture-Related Pre-Clinical Research

Cultural contexts weave through the fabric of pre-clinical research. This publication uncovers the cultural nuances influencing the design and execution of pre-clinical studies, shedding light on how diverse cultural perspectives impact the trajectory of CGT research in Asia.

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Manufacturing and Industry Evolution

The industrial heartbeat of cellular therapy in Asia is a testament to innovation and growth. "The ACTO Times" investigates how manufacturing practices, deeply entwined with cultural norms, contribute to the dynamic evolution of the CGT industry in this expansive region.

Regulatory Frontiers

The diverse regulatory frameworks and rich cultural tapestry across Asian regions stand as influential forces shaping the intricate process of CGT in the region. In navigating this dynamic landscape, each nation brings its own set of regulations, reflecting unique perspectives on ethical considerations, patient safety, and research practices.

OUR JOURNEY THROUGH TIME

IMAGE FROM CANVA.COM

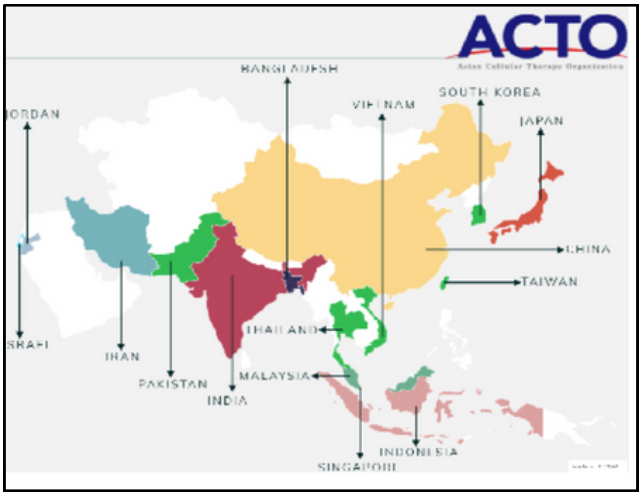
Over the years, the ACTO meetings became a cornerstone for professionals in the field, providing a platform for networking, sharing knowledge, and forging international partnerships. As the organization evolved, reflecting the dynamic landscape of CGT in the Asia-Pacific region.

The ACTO meeting was started from the first International Society of Cellular Therapy (ISCT) Asian-Pacific Regional Meeting 2010 in Japan. The primary objective of this gathering is to facilitate the exchange of knowledge and expertise among researchers, clinicians, business professionals, and regulators in the realm of CGT.

The focus is on advancements in equipment and treatments, encompassing areas such as expansion or modification for transplantation, immunotherapy, regenerative medicine, and gene therapy.

In many Asian regions, there has been limited exploration of expertise in innovative cellular therapy and the development of equipment for clinical purposes. Additionally, there is a notable absence of well-established regulatory guidelines for approval processes, which are crucial for fostering new ideas in clinical applications.

These challenges pose significant hurdles to the progress of our research initiatives. The intention is that this meeting will serve to improve communication among Asian professionals and foster collaborations with their Western counterparts, thereby contributing to overcoming these obstacles.



As of the present moment, the Asian Cellular Therapy Organization (ACTO) has seen the enthusiastic engagement of 15 regional territories in its annual meetings. This collective involvement underscores the organization's commitment to fostering collaboration and knowledge exchange among diverse regions within the realm of CGT. Joining ACTO provides an opportunity for regions to contribute their unique insights, experiences, and expertise to the ongoing discourse in CGT. As we embrace a spirit of inclusiveness, our shared journey towards scientific and medical advancements becomes even more robust and impactful.

IMAGE FROM CANVA.COM

The 16th ACTO 2025 Annual Congress in Singapore

2025 ACTO Annual Meeting on 14th - 16th August 2025

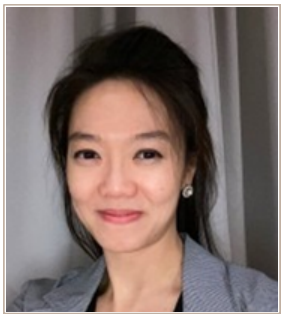
The Asian Cellular Therapy Organization is be holding its 16th annual congress (ACTO 2025) in Singapore, in partnership with **the SingHealth Duke-NUS Cell Therapy Centre** from the 14th to 16th August 2025.

This important event will focus on cell and gene therapy with an Asian perspective, addressing key regulatory issues, topics such as MSCs and Exosomes, and country-specific reports that highlight the latest developments in this vital
field across participating nations. The Asian region is marked by its genetic and cultural richness, alongside significant population dynamics, creating a unique environment for nuanced discussions.

Our organization prides itself on inclusivity, fostering collaboration among diverse stakeholders to drive robust and sustainable advancements in cell and gene therapy.
This in-person meeting will provide a valuable platform for collaboration across research, clinical, manufacturing, and regulatory realms. Attendees will have the opportunity to engage with leading experts and share insights that can shape the future of our industry.

PROFESSOR MICKEY B C KOH

DR SRINIVASAN KELLATHUR



DR FRANCESCA LIM

The 16th ACTO 2025 Annual Congress Programme

Tentative Programme

Day 1 - Thursday, 14 August 2025

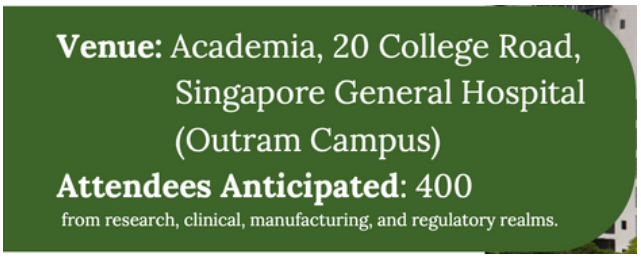
- Plenary Session
- CAR T Therapy Session
- Regenerative Medicine Session
- MSC Session
- Exosomes Session
- Parallel Luncheon Seminars
- Gene Therapy Session
- Immune Cell Therapy Session
- Evening Seminar

Day 2 - Friday, 15 August 2025

- Plenary Session
- Asian Report
- Luncheon Seminar
- ACTO Committee Meeting
- Regulatory Session with Roundtable Discussion
- Best abstract short presentation and Award
- Ceremony

Day 3 - Saturday, 16 August 2025

- Bioethics Session
- Patient Advocacy Workgroup
- Health Technology Assessment
- ACTO Report
- ACTRIS Site Visit



We're pleased by your interest in the 16th Annual Meeting of ACTO, set for 14-16 August 2025 in Singapore. Your participation would greatly enhance our gathering of distinguished professionals.

To register your interest and receive timely updates about the event, including website launch, early bird tickets, and call for abstracts, we invite you to complete our brief form. Your information will be handled confidentially and used solely for ACTO 2025 communications.

We look forward to potentially welcoming you to Singapore in 2025!

THE 16TH ACTO 2025 ANNUAL CONGRESS SPONSORSHIP PROSPECTUS

PLATINUM SPONSORSHIP

SGD$25,000 and above

- 60 minutes Luncheon Seminar.
- 30 minutes Oral Presentation during Sessions.
- Company Logo on Homepage of Conference Website, hyperlinked to company website.
- Company Logo on Conference Halls' main backdrop & the sponsor panel/s in venue, as per category.
- 3mx3m=9Sqm booth in Exhibition Area at the venue - bare space.
- Screening of <5 minutes corporate video during conference breaks.
- 20 complementary passes for conference.
- Post-Conference Attendee Analytics.
- Acknowledgment of your sponsorship at the conference opening & closing speech.

GOLD SPONSORSHIP

SGD$15,000 - $24,999

- 30 minutes Oral Presentation during Sessions.
- Company Logo on Homepage of Conference Website, hyperlinked to company website.
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- Screening of <5 minutes corporate video during conference breaks.
- 15 complementary passes for conference.
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- Company Logo on Conference Halls' main backdrop & the sponsor panel/s in venue, as per category.
- 3mx2m=6sqm booth in Exhibition Area at the venue -Octanorm shell scheme/bare space.
- 10 complementary passes for conference.
- Post-Conference Attendee Analytics.
- Acknowledgment of your sponsorship at the conference opening & closing speech.

BRONZE SPONSORSHIP

SGD$5,000-$9,999

- Company Logo on Homepage of Conference Website, hyperlinked to company website.
- Company Logo on Conference Halls' main backdrop & the sponsor panel/s in venue, as per category.
- 3mx2m=6Sqm booth in Exhibition Area at the venue -table top/bare space.
- 5 complementary passes for conference.
- Post-Conference Attendee Analytics.
- Acknowledgment of your sponsorship at the conference opening & closing speech.

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SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
Cell Therapy Centre

For futher enquiries, please contact:
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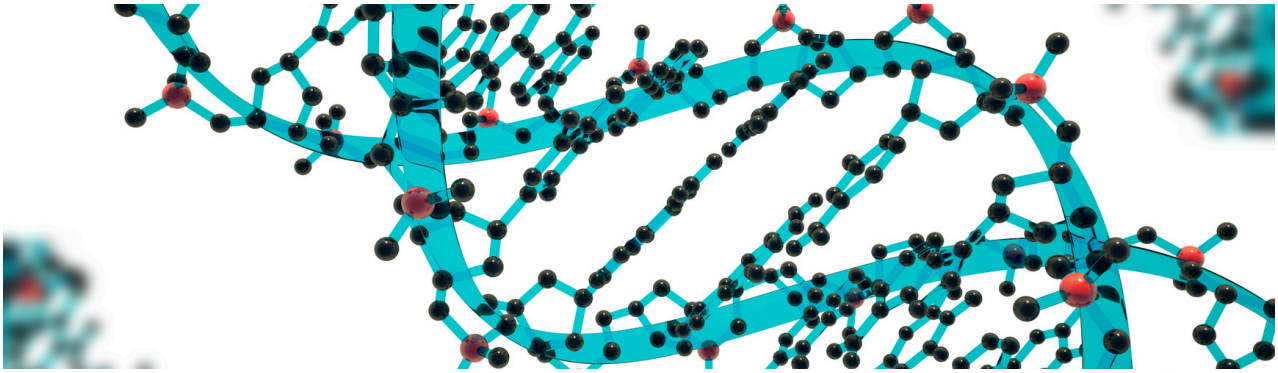

IMAGE FROM CANVA.COM

The Regulatory Landscape for Cell and Gene Therapies in Singapore. A Comprehensive Overview of the Health Sciences Authority's Regulatory Framework

Introduction

In Singapore, the Health Sciences Authority (HSA) meticulously categorizes cell and gene therapies into two distinct classes based on their level of manipulation, intended application, and integration with other therapeutic modalities or medical devices.

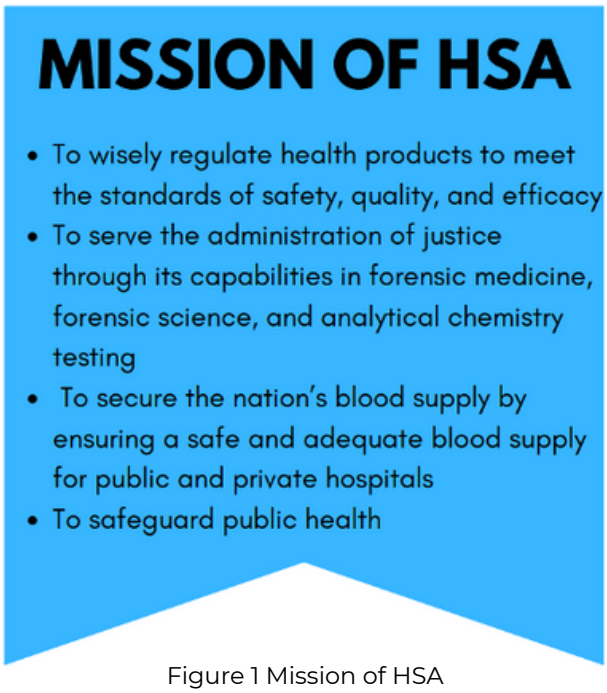

Figure 1 Mission of HSA

The HSA established a robust regulatory framework for cell and gene therapy products (CTGTPs) under the Health Products (CTGTP) Regulations 2021, underpinned by 11 supplementary legislative acts.

This framework differentiates CTGTPs into Class 1 (lower risk) and Class 2 (moderate to high risk) based on their inherent risk profiles.

This approach facilitates the streamlined development and registration of CTGTPs while concurrently ensuring stringent adherence to safety, quality, and efficacy standards, thereby fostering innovation within the field of CTGTP development.

Globally, cell and gene therapies represent a burgeoning frontier in therapeutic medicine.

Regulatory authorities worldwide are actively developing regulatory frameworks to ensure strict adherence to universal ethical principles and global best practices in the development of these transformative therapies.

Cell and gene therapies present a unique set of challenges, encompassing safety concerns, intricate ethical considerations, and the potential for unforeseen adverse events.

The CTGTP regulatory framework for Singapore was officially enacted under the Health Products Act and Poisons Act on February 17, 2021, and became operational on March 1, 2021.

Updates on CGT Regulation

Table 1 Legislations for CTGTP

S103	Health Products Act (Amendment of first schedule) order 2021
S104	Health Products (Cell, tissue, and gene therapy products) Regulations 2021
S105	Health Products (Existing manufacturers of CTGT products – exemption) Order 2021
S106	Health Products (Licensing of retail pharmacies) (amendment) Regulations 2021
S107	Health Products (Clinical trials) (amendment) Regulations 2021
S108	Health Products (Therapeutic products as clinical research materials) (amendment) Regulations 2021
S109	Health Products (Advertisement of Therapeutic products) (amendment) Regulations 2021
S110	Health Products (Exemptions) (amendment) Order 2021
S111	Health Products (Medical Devices) (amendment) Regulations 202
S112	Poisons (amendment) Rules 2021
S450	Health Products (Fees) regulations 2022

This comprehensive framework provides a precise definition of cell and gene therapy products while explicitly excluding the following:

- Recombinant vaccines designed for prophylactic purposes.
- in vitro diagnostic modalities.
- Human bone marrow, peripheral blood, or umbilical or placental cord blood subjected to minimal manipulation and intended for homologous utilization.
- Cells and tissues procured from a patient, subjected to minimal manipulation, and re-implanted for homologous utilization in the same patient during the same surgical procedure.
- Organs and tissues subjected to minimal manipulation and intended for transplantation.
- Reproductive cells (sperm, ova) and embryos intended for assisted reproductive technologies.
- Whole blood and any blood component subjected to minimal manipulation and intended for the management of blood loss or blood disorders.

The framework meticulously categorizes CTGTPs into two distinct classes.

- Class 1 CTGTPs are low-risk products derived from minimally manipulated biological materials for homologous utilization and are not combined or conjugated with other therapeutic modalities or medical devices. Illustrative examples include demineralized human bone matrix and bone allografts for orthopedic indications, amniotic membrane utilized as a corneal surface barrier, and donated skin for burn wound coverage.
- Class 2 CTGTPs encompass moderate to high-risk products that do not fulfill the criteria for classification as Class 1 products and encompass those containing viable animal cells and recombinant nucleic acids. Illustrative examples include cultured chondrocytes for cartilage repair, chimeric antigen receptor T cells for hematological malignancies, bone marrow-derived stem cells for cardiac repair, and xenogeneic products (products containing viable animal cells/tissues).

Regulatory Pathways and Requirements for Class 1 CTGTPs

- The Advanced Therapy Products Branch of the HPRG (HSA) mandates notification of any Class 1 CTGTP product and requires written approval for distribution.
- Applicants are required to submit an application containing:
  - A duly certified true copy of a valid accreditation certificate (e.g., AABB, AATB, FACT, CAP).
  - Concrete evidence demonstrating that the establishment is registered with the country's relevant regulatory authority.
  - Precise product release specifications or a Certificate of Analysis.
  - Product labels incorporating information pertaining to the product's shelf life and container closure.
- The HSA will conduct a thorough review of the application within a 14-day timeframe.
- The HSA will promptly notify the applicant of any identified deficiencies within the application.
- Upon favorable evaluation and subsequent approval for distribution, the HSA will formally notify the applicant and subsequently list the product on the HSA's official website.

Table 2 Risk classification of CTGTPS (Lee Lee Ong, 2023)

Classification	Degree of manipulation	Intended use	Combination or use with therapeutic products or medical device
Class 1 CTGTP	Minimal	Homologous	No
Class 2 CTGTP	More than minimal	Non-homologous	Yes
	More than minimal	Non-homologous	No
	More than minimal	Homologous	Yes
	More than minimal	Homologous	No
	Minimal	Non-homologous	Yes
	Minimal	Non-homologous	No

Updates on CGT Regulation

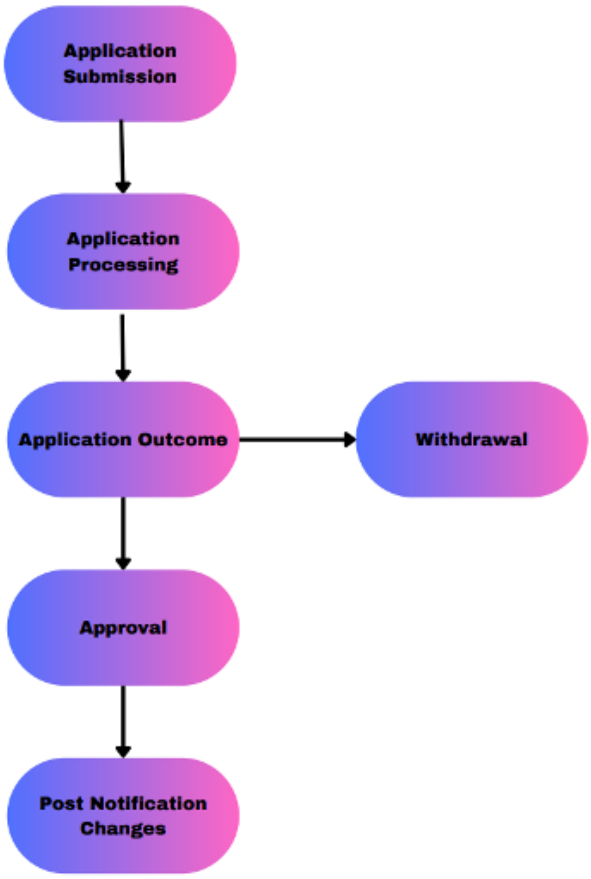

Figure 2 Notification process for Class 1 CTGTPs

Regulatory Pathways and Requirements for Class 2 CTGTPs

- Class 2 products necessitate formal registration prior to market distribution.
- Applicants have the option to seek expert guidance on their application dossier through a consultative meeting prior to formal submission.
- Registration for Class 2 products can proceed via a comprehensive evaluation pathway (for products not previously approved by an HSA-comparable overseas regulatory authority) or an abridged evaluation pathway (for products previously approved by an HSA-comparable overseas regulatory authority).
- The application dossier must encompass comprehensive documentation, including a Singapore-specific annex outlining a proposed pharmacovigilance plan and risk mitigation strategies.
- The HSA implements a screening period of approximately 50 days to meticulously assess the completeness of submitted documents and datasets.
- Target evaluation timelines are established at 270 days for comprehensive applications and 180 days for abridged applications.

The product registrant assumes ultimate responsibility for ensuring the quality.

Conditional Registration Pathway

- A conditional registration pathway is available for CTGTPs that:
- Are specifically intended to address unmet medical needs.
- Have demonstrated a favorable safety profile in early-phase clinical trials.
- Exhibit preliminary data indicating substantial therapeutic benefit relative to existing standard-of-care treatment options.

Dealer Requirements

- Dealers handling minimally manipulated CTGTPs are not subject to licensing requirements but are mandated to submit a dealer's notification application prior to commencing manufacturing, importation, or wholesaling activities.

Table 3 Types of application (Lee Lee Ong, 2023)

Application type	Conditions
NDA- 1	For the first strength of a product containing a new CTGTP. This means the CTGTP is currently not registered in Singapore
NDA- 2	(a) For the first strength of a product containing New combination of registered CTGTP Registered CTGTP in either of the following: New dosage form, such as capsules and injectables New presentation, such as single-dose vials, multi-dose vials, and pre-filled syringes New formulation, such as preservative-free. Registered CTGTP for use by a new route of administration (b) For products do not fall under the requirements for NDA-1 or NDA-3
NDA- 3	For subsequent strengths of a product that has been registered or submitted as an NDA-1 or NDA-2. The product name, dosage form, indication, dosing regimen, and patient population should be the same as that for the NDA-1 or NDA-2 submission.

- They are obligated to comply with:
  - Stringent good tissue practices.
  - Quality standards as outlined in the Singapore Standard for Good Distribution Practice for Medical Devices (SS 620).
  - ISO 13485:2016: Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes.
  - HSA Guidance Notes on Good Distribution Practice.
- Entities dealing with more than minimally manipulated CTGTPs are required to obtain the necessary licenses.
- All domestic manufacturers are mandated to possess a valid manufacturer's license for CTGTPs and are required to adhere to Good Manufacturing Practices (GMP) guidelines as outlined by the HSA.
- Importers and wholesalers are obligated to adhere to stringent good distribution practices.
- In-house manufacturing of unregistered Class 2 CTGTPs by local healthcare institutions or contract manufacturers is subject to rigorous regulatory oversight.

Figure 3 Comparable overseas regulators of the HSA

Clinical Trials

- Clinical trials involving Class 1 CTGTPs are not subject to direct regulatory oversight by the HSA but are required to comply with the provisions outlined in the Human Biomedical Research Act and its associated Regulations.
- Clinical trials involving locally unregistered Class 2 CTGTPs or unapproved applications of locally registered Class 2 CTGTPs necessitate a Clinical Trial Authorization (CTA).
- The target evaluation timeframe for CTAs is established at 60 days.
- Clinical Trial Notifications (CTNs) are required for clinical trials conducted utilizing locally registered Class 2 CTGTPs in strict accordance with their approved labeling.
- The target evaluation timeframe for CTNs is established at 5 days.

Import and Supply

- The importation and distribution of Class 2 CTGTPs upon request from qualified healthcare practitioners for utilization on their patients are subject to stringent regulatory controls.
- The Special Access Route may be considered for unregistered products that have received prior approval from an HSA-comparable overseas regulatory authority.
- The distribution of Out of Specification (OOS) products may be considered under exceptional circumstances for clinical trials and clinical utilization to avert an immediate and substantial risk to the patient's well-being.

All guidance documents, including relevant forms and templates, are readily accessible on the HSA's official website to assist stakeholders in fulfilling the regulatory requirements pertaining to CTGTPs.

Cell and gene therapy research in Singapore has significantly advanced. The CTGTP regulations provide clarity for stakeholders, guiding risk-based oversight. These regulations empower the HSA to foster innovation while ensuring patient safety in this evolving field

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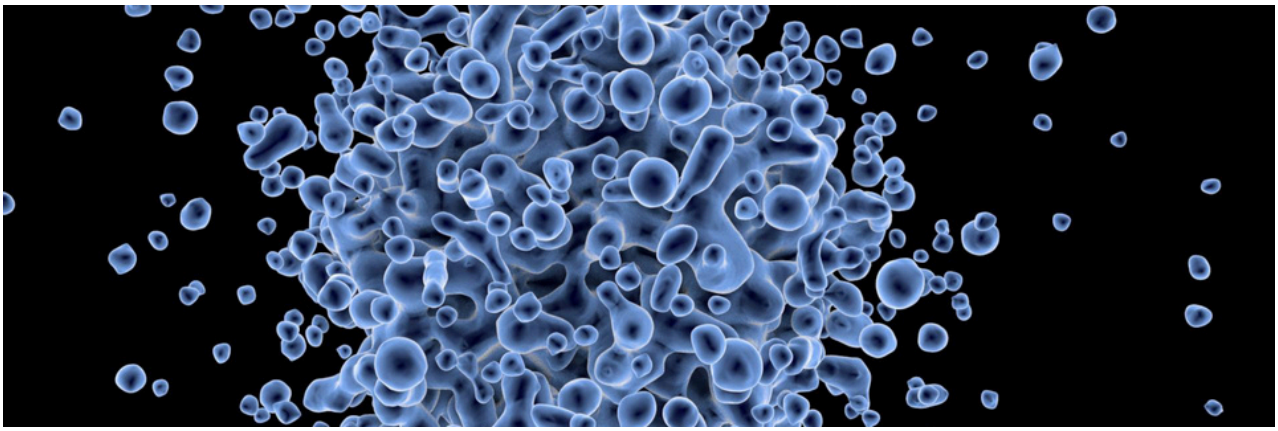

IMAGE FROM CANVA.COM

Current Mechanisms and Future Trends of Mesenchymal Stem Cell (MSC) Therapies: Bridging Clinical Applications and Emerging Innovations

Mesenchymal stem cell (MSC) therapies have gained significant momentum in regenerative medicine, with expanding clinical applications and notable regulatory approvals worldwide. Over the past decade, multiple MSC-based products have achieved approval for treating diverse conditions, reflecting the growing confidence in their safety and efficacy. Key breakthroughs include Ryoncil (approved by the US FDA in 2024 for steroid-refractory graft-versus-host disease [SR-GvHD]), Temcell (approved in Japan in 2015 for acute GvHD), and Alofisel (approved in the EU and Japan in 2018 for complex perianal fistulas in Crohn's disease). Other notable approvals include Cartistem in South Korea for osteoarthritis and Stemirac in Japan for spinal cord injury. In 2025, China's Amimestrocel (Ruibosheng) was approved by the National Medical Products Administration (NMPA) for the treatment of steroid-refractory GvHD (SR-GvHD), marking another significant milestone in MSC therapy development. These approvals highlight the versatility of MSCs in modulating immune responses, reducing inflammation, and promoting tissue repair in various disease settings. As of 2025, global MSC clinical trials continue to explore additional applications in autoimmune diseases, cardiovascular disorders, musculoskeletal conditions, and pulmonary diseases, reflecting sustained interest in expanding the therapeutic potential of MSCs. However, despite these advances, challenges remain in achieving consistent clinical outcomes due to the heterogeneity of MSC sources, donor variability, and differences in manufacturing protocols.

Addressing these challenges will be crucial for maximizing the potential of MSC-based therapies and ensuring their widespread clinical adoption.

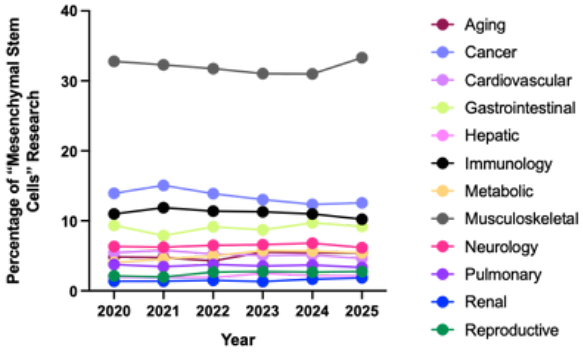

Figure 1. Distribution of MSC-related research across various disease fields from 2020 to 2025 based on PubMed search data.

The number of MSC-related publications from 2020 to 2025 reflects sustained interest across a broad range of indications. Notably, musculoskeletal disorders—remain the most intensively studied areas, highlighting the consistent focus on MSCs for regenerative medicine applications.

In addition to musculoskeletal conditions, a stable volume of research has also been directed toward autoimmune diseases.

Although less dominant in publication volume, neurological and gastrointestinal diseases have maintained steady research interest, indicating emerging potential for MSC-based interventions in neuroregeneration and gut-immune regulation

Overall, the trend suggests MSCs are increasingly recognized not only for tissue repair but also for immune homeostasis and chronic disease management.

From a mechanistic perspective, MSCs exert their therapeutic effects through both paracrine signaling and cell-to-cell contact mechanisms, modulating the immune system and promoting tissue regeneration. In GvHD, MSCs inhibit alloreactive T-cell proliferation by secreting IDO and PGE2, while enhancing Treg expansion, thereby reducing inflammation and preventing tissue damage [1, 2]. Additionally, MSCs attenuate macrophage-mediated inflammation by promoting the M1-to-M2 phenotype switch through TNF-stimulated gene 6 (TSG-6) and hepatocyte growth factor (HGF) secretion, a mechanism that is pivotal in controlling excessive inflammation in autoimmune diseases like RA and SLE [3, 4]. In musculoskeletal disorders such as osteoporosis and bone fractures, MSCs promote osteogenesis by secreting vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP-2), and insulin-like growth factor-1 (IGF-1), which stimulate endothelial proliferation and promote differentiation of MSCs into osteoblasts, enhancing bone matrix deposition and repair [5]. Furthermore, in skin wound healing, MSCs accelerate epithelial regeneration by secreting keratinocyte growth factor (KGF), epidermal growth factor (EGF), and matrix metalloproteinases (MMPs), facilitating tissue remodeling and promoting re-epithelialization [6].

In cardiovascular disorders such as myocardial infarction (MI) and atherosclerosis, MSCs secrete VEGF, HGF, and IGF-1, which promote neovascularization and protect cardiomyocytes from apoptosis, while inhibiting fibrosis by modulating TGF-β1/Smad3 signaling [7]. In pulmonary disorders such as acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD), MSCs secrete IL-10 and TSG-6, reducing lung inflammation, mitigating fibrosis, and enhancing alveolar epithelial repair [8]. Moreover, in metabolic disorders such as diabetic wound healing and metabolic syndrome, MSCs exert antioxidant and anti-inflammatory effects by reducing oxidative stress and inhibiting pro-inflammatory cytokines. They promote tissue repair through the secretion of SOD (superoxide dismutase), glutathione peroxidase (GPX), and other antioxidant enzymes, enhancing tissue regeneration in diabetic-associated diseases [9].

Recent advancements in MSC research have focused on improving their therapeutic potential through genetic modification and bioengineering approaches. Genetically modified MSCs have been engineered to overexpress key cytokines such as IL-10, IDO, and VEGF, enhancing their immunomodulatory and regenerative efficacy in preclinical and clinical models [10-12].

Moreover, advances in 3D culture systems and bioreactor technologies have improved MSC expansion and maintained their therapeutic properties by mimicking the native microenvironment [12]. Hypoxia preconditioning has emerged as another promising strategy to enhance MSC survival and paracrine activity, boosting their regenerative potential in ischemic and inflammatory conditions [13]. Additionally, the integration of single-cell transcriptomic analysis and AI-based predictive models is revolutionizing the identification of MSC subpopulations with enhanced therapeutic potency, paving the way for more precise and personalized MSC therapies. These innovations collectively address the challenges associated with MSC heterogeneity and batch-to-batch variability, ensuring more consistent and effective clinical outcomes.

In conclusion, MSC therapies have demonstrated tremendous potential in modulating immune responses and promoting tissue regeneration across a wide range of diseases. With continued research into engineered MSCs, EV-based therapies, and AI-driven quality control, the future of MSC-based treatments appears promising. As these technologies are integrated into clinical practice, MSC therapies will not only address existing challenges in cell-based therapies but also open new avenues for treating complex and chronic conditions, ultimately transforming the landscape of regenerative medicine.

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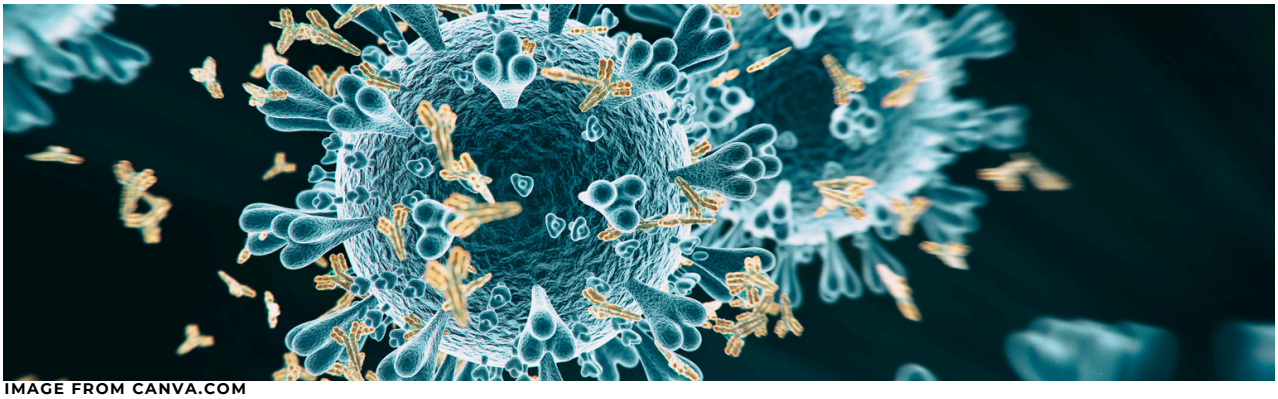

IMAGE FROM CANVA.COM

The FDA's Shift Away from Animal Testing: The Role of Organoid Models in Monoclonal Antibodies and Drug Development

The U.S. Food and Drug Administration (FDA) has announced a groundbreaking shift in biomedical research by phasing out animal testing requirements for monoclonal antibodies and other drugs. This transition aims to accelerate drug development, improve safety assessments, and reduce reliance on animal models. However, concerns remain regarding the readiness of alternative models, particularly human organoids, to fully replace traditional animal testing.

Organoids are three-dimensional, miniaturized versions of human organs cultivated in vitro from stem cells. These structures self-organize to mimic the architecture and functionality of actual human organs, making them invaluable tools in biomedical research. Unlike traditional cell cultures, organoids provide a more physiologically relevant environment, enabling researchers to study complex biological interactions in ways that were previously unattainable.

The application of organoids spans various fields of medical research. They have been instrumental in studying disease mechanisms, drug testing, and regenerative medicine. For instance, intestinal organoids have provided insights into gastrointestinal disorders, while brain organoids have helped researchers understand neurological conditions such as Alzheimer's and autism. Additionally, liver and kidney organoids are being used to evaluate drug toxicity, offering a promising alternative to animal models.

The FDA's new regulatory framework encourages the use of New Approach Methodologies (NAMs), which include AI-based computational models, cell lines, and organoid toxicity testing. The agency aims to refine, reduce, and potentially replace animal testing by leveraging human-relevant models. Implementation has begun with investigational new drug (IND) applications, where NAMs data is encouraged.

FDA Commissioner Martin A. Makary emphasized that this initiative represents a 'paradigm shift in drug evaluation', allowing safer treatments to reach patients faster while reducing research and development costs. The agency will also incorporate real-world safety data from other countries with comparable regulatory standards, further minimizing the need for animal trials.

While organoid models hold immense promise, several challenges must be addressed before they can fully replace animal testing:
1. Scalability and Standardization – Variability in organoid models remains a concern, as differences in cell sources and culture conditions can affect reproducibility.
2. Multi-Organ Interactions – Organoids currently lack the ability to fully simulate complex physiological interactions between multiple organ systems.
3. Immune System Dynamics – While organoids can replicate many aspects of human physiology, they do not yet fully integrate immune responses, which are crucial for drug safety assessments.

4. Regulatory Acceptance – The FDA's endorsement of organoid-based testing is a significant step, but further validation and refinement are necessary for widespread adoption.

Looking ahead, organoid technology is expected to play a pivotal role in regenerative medicine, artificial organ development, and gene therapy. Scientists envision a future where lab-grown organoids could serve as transplantable tissue sources, reducing dependency on donor organs. Additionally, bioengineering advancements could allow organoids to be integrated with microfluidic systems, forming organ-on-a-chip models that simulate entire physiological networks.

Continued investment in research, technological refinement, and interdisciplinary collaboration will be critical to overcoming current limitations. As scientific advancements push the boundaries of preclinical testing, organoids remain at the forefront, offering a transformative yet evolving approach to improving drug development and safety assessments.

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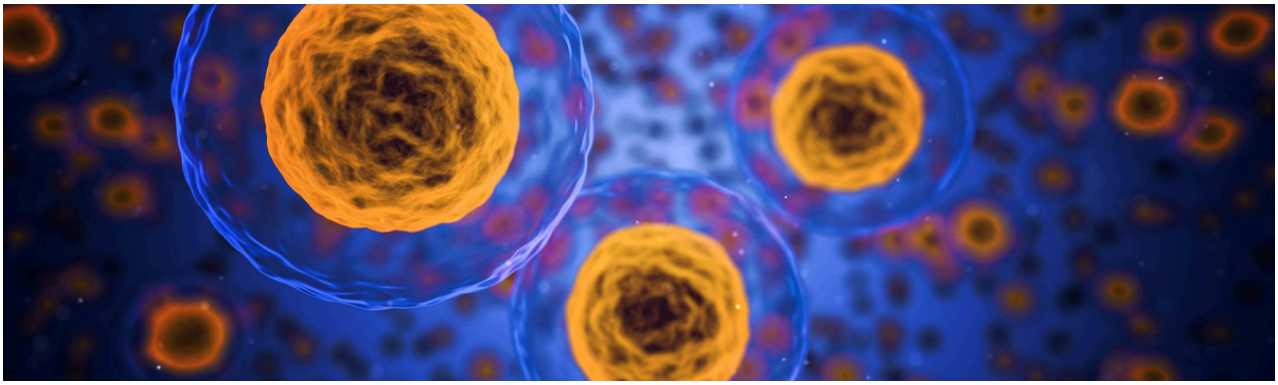

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Recent Clinical Application of Extracellular Vesicles (EVs)

Introduction

Extracellular vesicles (EVs), including exosomes, microvesicles, and apoptotic bodies, are membrane-bound particles that are naturally secreted by cells into the extracellular space. EVs are widely recognized for their crucial role in intercellular communication, as they mediate the transfer of proteins, lipids, and nucleic acids between cells. This transfer of molecular cargo facilitates the regulation of various physiological and pathological processes, including immune modulation, tissue repair, and tumor progression (Terai et al., 2025).

The therapeutic potential of EVs lies in their ability to act as delivery vehicles, capable of carrying and releasing therapeutic agents such as proteins, small molecules, and genetic material to specific target cells. Their inherent biocompatibility, ability to cross biological barriers, and potential to modulate biological processes make them highly attractive for use in regenerative medicine and as part of drug delivery systems (Terai et al., 2025).

As EV-based therapies continue to develop, it is crucial to ensure their safety, quality, and efficacy. This comprehensive review summarizes the guidance provided in the Guidance on the Clinical Application of Extracellular Vesicles (Terai et al., 2025), focusing on the critical aspects of EV production, risk profiling, regulatory compliance, and clinical applications.

Key Considerations for EV-Based Therapies

Risk Profiling in EV-Based Therapies: A critical first step in developing EV-based therapies is identifying potential risks. As EVs are derived from biological sources, their clinical use carries several inherent risks that must be addressed to ensure patient safety and therapeutic efficacy:

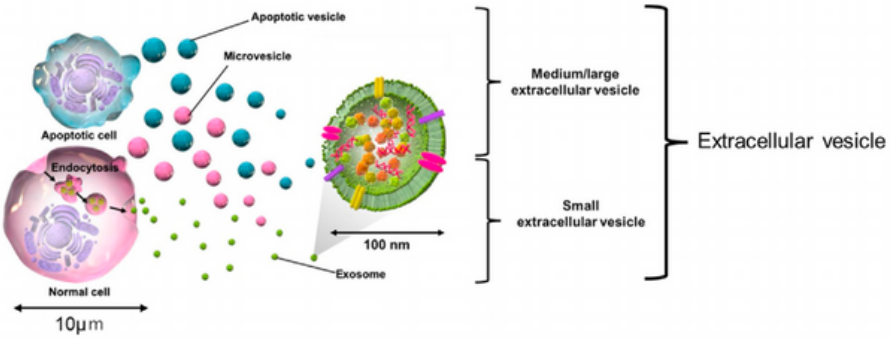

Figure 1. Extracellular vesicles (EVs), including exosomes and other types of vesicles, are substances released by cells. These vesicles carry growth factors that promote tissue regeneration and molecules involved in intercellular signaling. EVs are crucial for communication between cells and have potential therapeutic applications for a variety of diseases (Terai et al., 2025).

- Infectious Contamination: EV preparations are susceptible to contamination from viruses, bacteria, fungi, or mycoplasma during their isolation, production, and storage. Ensuring that EVs are produced in sterile, controlled environments, and that all raw materials are tested for contaminants, is essential to prevent adverse reactions in patients. Additionally, specific guidelines recommend the use of sterile filtration methods and regular microbial testing at various stages of EV preparation (Lener et al., 2015).
- Immunogenicity: While EVs are typically derived from autologous cells or closely matched donor cells, there is still a risk that foreign EV components could elicit an immune response in the recipient. This is particularly true if the EVs are modified genetically or contain surface markers not typically present in human cells. Immunogenicity could lead to immune rejection or the triggering of autoimmune responses. Comprehensive testing for immunogenicity and cytokine profiling is recommended to minimize such risks (Théry et al., 2018).
- Impurities and Contaminants: Residual proteins, nucleic acids, or cellular debris present in the final EV preparations may compromise their safety and therapeutic activity. Strict purification protocols are required to isolate EVs and remove non-EV contaminants, such as proteins or lipids from the cellular membrane. These impurities can be harmful, potentially causing immune activation or toxicity (Gimona et al., 2021).
- Biodistribution and Toxicity: One of the greatest challenges in EV therapy is understanding how EVs distribute within the body. EVs may accumulate in organs such as the liver, spleen, or lungs, where they could cause toxicity. Preclinical animal studies are crucial to mapping the biodistribution of EVs and ensuring that they reach the target tissues without causing harm to other organs. Monitoring of EVs post-administration in clinical trials is essential to determine their pharmacokinetics and any potential toxic effects (Lener et al., 2015).

Manufacturing Processes and Quality Control

To move EV-based therapies into clinical practice, the manufacturing of EVs must meet rigorous standards. Ensuring the consistent production of high-quality EVs is essential to maintaining the safety and efficacy of EV therapies. Key considerations in manufacturing include:

- Aseptic Processing: The entire production process of EVs—from the isolation of the source cells to the final EV preparation—must occur under aseptic conditions to prevent microbial contamination. This includes using sterile equipment, maintaining clean room environments, and implementing contamination control measures (Tsuchiya et al., 2022).
- Standardization of EV Isolation and Purification: Variability in EV production is one of the biggest challenges in clinical translation. To ensure that every batch of EVs meets the same quality and potency, standardized protocols must be developed for the isolation, purification, and characterization of EVs. These protocols should outline methods for cell culture, EV isolation (such as ultracentrifugation, filtration, or affinity capture), and purification processes to ensure product consistency across different production runs (Théry et al., 2018).
- Quality Control and Validation: Quality control is critical to ensuring the safety and efficacy of EV-based therapies. This includes the regular testing of EV preparations for sterility, endotoxin levels, EV marker presence (e.g., CD9, CD63, TSG101), and other biochemical characteristics. The use of well-established assays for potency evaluation and validation of the therapeutic effects of EVs is also essential to confirm their biological activity before clinical use (Lener et al., 2015).

- Xeno-Free Culture and Synthetic Serum Substitutes: To minimize the risk of contamination from animal-derived components, the guidance recommends using xeno-free culture media and synthetic serum substitutes, such as knockout serum replacements. This approach ensures that the EV preparations are entirely human-derived, reducing the risk of animal protein contamination and associated immunological reactions (Tsuchiya et al., 2022).

Electron Microscopy: Electron microscopy allows for high-resolution imaging of the EVs, providing detailed visual confirmation of their morphology. This technique is useful for confirming the size, shape, and membrane integrity of EVs, ensuring that they are structurally intact and consistent with the intended product (Lener et al., 2015).

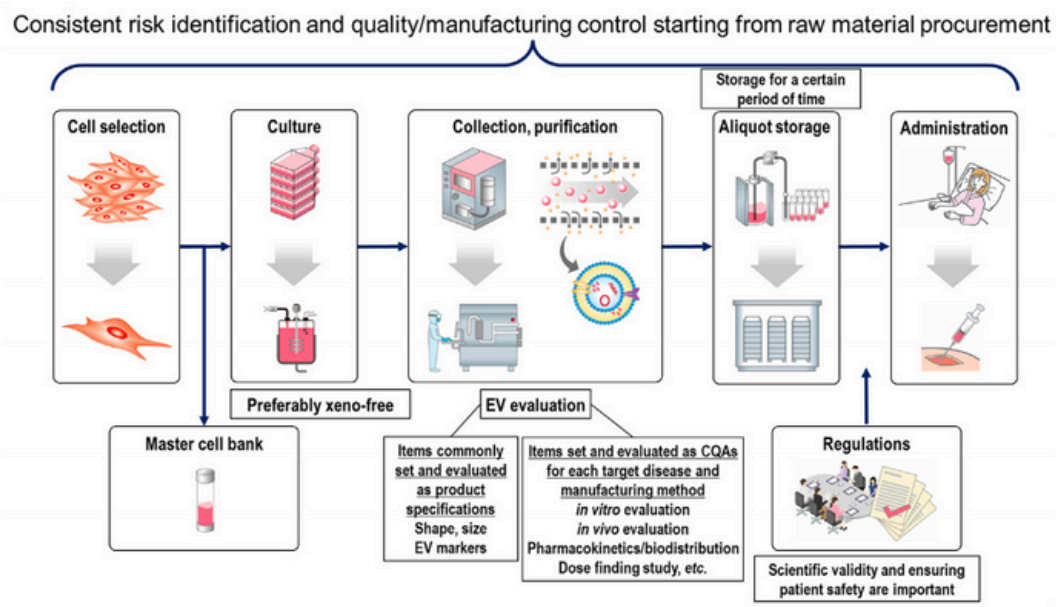

Figure 2. The scope of guidance on the clinical application of EVs (Terai et al., 2025).

Verification and Efficacy Validation

Verification of the identity and quality of EV preparations is crucial for clinical application. This involves confirming the presence of key EV-specific markers and ensuring that the EVs retain their functional properties. Several techniques are employed for this purpose:

- Nano-Flow Cytometry: This technique is used to analyze the size and surface markers of EVs, providing valuable information on their quantity and composition. By assessing specific markers like CD9, CD63, and CD81, nano-flow cytometry allows for a detailed profile of EV preparations, ensuring that they meet the required standards (Théry et al., 2018).
- Western Blotting and Proteomics: These techniques help identify and quantify the proteins present in EV preparations. Western blotting and proteomic analysis can be used to profile EV-specific proteins and determine whether the EVs contain the therapeutic cargo intended for delivery (Gimona et al., 2021).

To validate the efficacy of EVs as therapeutic agents, preclinical in vitro and in vivo studies are essential. These studies assess the biological activity of EVs, including their ability to target specific cells, deliver therapeutic agents, and produce the desired therapeutic outcomes. These validation steps help ensure that the EVs are effective and safe for human use.

Japanese Regulatory Framework for EV-Based Therapies

Japan has established its own set of regulatory guidelines to ensure the safe application of EV-based therapies, which are crucial for the clinical translation of these promising treatments. These guidelines are provided by the Japanese Society for Regenerative Medicine (JSRM) and the Japanese Society for Extracellular Vesicles (JSEV). The regulatory framework emphasizes the following points (Tsuchiya et al., 2022):

- Regulatory Compliance: EV-based products must adhere to Japan's regulatory requirements, particularly those set by the Ministry of Health, Labour, and Welfare (MHLW). This includes obtaining approval for clinical trials, manufacturing licenses, and ensuring that products comply with safety and efficacy standards.
- Clinical Trial Standards: EV therapies must undergo rigorous clinical trials before they can be approved for widespread use. These trials are governed by international good clinical practice (GCP) standards and must demonstrate the safety and therapeutic benefit of EVs in human subjects.
- Manufacturing Standards: EVs must be produced in facilities that meet Good Manufacturing Practices (GMP). These standards ensure that EV preparations are consistent, safe, and free from contaminants.
- International Collaboration: Japan encourages international collaboration in the regulation of EV-based therapies to promote consistency and streamline the approval process. Harmonization of regulatory standards at the global level will facilitate the worldwide use of EVs as therapeutic agents (Lai et al., 2023).

Conclusion

Extracellular vesicles represent an exciting frontier in regenerative medicine, offering innovative treatment options for various diseases. However, their safe and effective clinical application requires rigorous regulatory oversight, comprehensive risk management, and adherence to stringent manufacturing and quality control protocols. The guidelines set forth by the Japanese Society for Regenerative Medicine (JSRM) and the Japanese Society for Extracellular Vesicles (JSEV) provide a robust framework for the clinical use of EVs, ensuring that these therapies are developed and applied in a safe and standardized manner. As research advances and regulatory frameworks are harmonized globally, EV-based therapies have the potential to transform the landscape of regenerative medicine.

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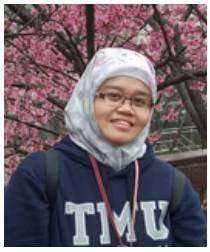

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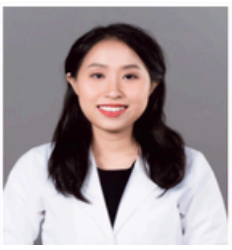

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