The ACTO Times

Asian Cellular Therapy Organization

VOL. 02
ISSUE 01

UPDATES OF CGT CLINICAL TRIALS

ACADEMIC HIGHLIGHT

ACTO MEETING 2024 REPORT

2025 NEW YEAR EDITION

Greetings
The ACTO Chairperson

Dear ACTO members,

We are pleased to share the New Year edition of The ACTO Times 2025, the second annual electronic magazine for ACTO's global connection in cell and gene therapy (CGT).

The Asian Cellular Therapy Organization (ACTO) was founded in 2010 to support Asia's scientific community. Established by experts from across Asia, ACTO serves as an accessible alternative to ISCT.

Since our first meeting in Japan, led by Dr. Yoichi Takaue, we have successfully invited leaders from Taiwan, Singapore, Israel, Korea, Thailand, Iran, and China to create a platform tailored to the unique needs of the Asian region. ACTO has hosted 15 annual meetings since 2010 across Asia, uniting academia, industry, and regulatory agencies to advance new therapies for patients.

In 2024, ACTO held its Annual Meeting in Hangzhou, China, focusing on the latest advances in blood cancer therapy. We extend our gratitude to VP Dr. He Huang and his outstanding team for their support. Another significant milestone is the establishment of our electronic magazine, The ACTO Times, led by Editor-in-Chief Distinguished Prof. Rita Yen-Hua Huang of Taipei Medical University. She has made remarkable contributions by publishing three editions (Spring, Summer, and Autumn), gathering updates from 15 Asian territories on advanced cell and gene therapy (CGT) from regulatory and industry committees.

As we enter 2025, we sincerely thank ACTO Vice President Dr. Mickey Koh and Industry Committee Chairman Dr. Kellathur N. Srinivasan and their team for hosting the 2025 ACTO Annual Meeting in Singapore. We warmly invite all ACTO members to join us in Singapore.

Once again, we truly appreciate your invaluable contributions in making The ACTO Times a key resource for our members. Thank you for your support and involvement.

Happy New Year!

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 excited to present the 2025 New Year Edition, featuring a completely new magazine layout that includes both a Spotlight Panel and an Academia Panel. This edition conveys our heartfelt greetings for the new year and highlights the global progress in cell and gene therapy (CGT) throughout 2024.

The year 2024 marks a significant milestone in CGT, with notable advances in oncology therapy, gene therapy, and tissue engineering. The FDA approved TIL and TCR immune cell therapies for solid tumors, and Kite Pharma's CAR-T therapy was approved as a first-line treatment option for high-risk large B-cell lymphoma.

Furthermore, CAR-T therapy has demonstrated breakthrough potential in treating solid cancers and autoimmune diseases. Currently, there are seven CAR-T products approved by the FDA, six approved by the EMA, and four approved in China.

In gene therapy, 2024 showcased significant advancements with innovative treatments for various genetic disorders. Casgevy emerged as a promising therapy for transfusion-dependent beta-thalassemia (TDT), while Lenmeldy was introduced for metachromatic leukodystrophy (MLD). Beqvez gained attention for its application in severe hemophilia B. Additionally, Autoleucel, a gene-edited autologous T-cell therapy, demonstrated efficacy in treating unresectable or metastatic synovial sarcoma, highlighting the potential of gene editing in oncology. Kebilidi was recognized for its role in treating AADC deficiency, marking a significant step forward in gene therapy for rare neurological conditions.

Notably, the FDA approved its first non-cell tissue engineering product, SYMVESS, in 2024. This acellular tissue-engineered vessel is designed for the treatment of unmet extremity vascular trauma.

2024 marked a significant milestone for mesenchymal stem cells (MSC) in the United States. The FDA approved the allogeneic bone marrow MSC product Mesoblast Ryoncil (generic name Remestemcel-L) for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients. On January 2, 2025, China granted its first conditional approval for a human umbilical cord MSC product, Ruibosheng, for the same indication. Additionally, a noteworthy development was the withdrawal of Alofisel, an allogeneic adipose-derived mesenchymal stem cell product, from the European Union market due to the determination that the risks outweighed the potential benefits.

Editor's Column
The ACTO Times Editor-in Chief

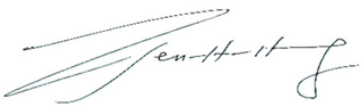
In 2024, ACTO hosted the ACTO Annual Meeting in Hangzhou, China, showcasing advancements in hematology and CAR-T therapy. We extend our gratitude to ACTO VP Dr. He Huang and his outstanding team for their support during the event. I am also pleased to share that The ACTO Times has made significant progress this year, successfully coordinating efforts across 15 Asian territories for CGT, with a spotlight on Indonesia, India, and Taiwan, addressing CGT regulation, clinical trials, and industry development. Our expert columns covered topics including CAR-T, EV/exosomes, iPSCs, and regulations.

As we welcome the new year in 2025, we extend a warm invitation from Singapore for the upcoming 2025 ACTO Annual Meeting. We sincerely thank ACTO Vice President Dr. Mickey Koh and Industry Committee Chairman Dr. Kellathur N. Srinivasan, along with their team, for hosting the meeting. We invite you to join us!

I am also pleased to introduce our new members of the Editorial Office: Yu-Xiu Tony Lin, D. Renovaldi, and Vijetha Karen Kitchley. I greatly appreciate their efforts in making the New Year Edition a success.

Once again, I would like to express my heartfelt appreciation for your invaluable support of The ACTO Times. Wishing you a healthy and prosperous New Year in 2025!

Sincerely,
Rita Yen Hua Huang



Yen Hua (Rita) Huang

Distinguished Professor,
Taipei Medical University, Taipei

ACTO Executive Committee

Chairperson

Akihiro Shimosaka, Tokyo

Vice President

Abbas Ghaderi, Shiraz
Abdalla Awidi Abbadi, Jordan
Bin Koming Ya'Akop, Kuala Lumpur
Chi Dung Phu, Ho Chi Min
Ferry Sandra, Jakarta
He Huang, Hangzhou
Hee-Je Kim, Seoul
Jun Ren, Shanghai
Kai-Yan Liu, Beijing
Keiya Ozawa, Tochigi
Khattry Navin, India
Mickey Koh, Singapore
Mohiuddin Ahmed Khan, Dhaka
Saengsuree Jootar, Bangkok
Yao-Chan Chen, Taipei

Past President of the ACTO Annual Meeting

Yoichi Takaue, Miyazaki (2010)
Mine Harada, Miyazaki (2011)
Saengsuree Jootar, Bangkok (2012)
Yao-Chan Chen, Taipei (2013)
Teruo Okano, Osaka (2014)
Hee Young Shin, Gwangju (2015)
Xiao-Jun Huang, Beijing (2016)
Keiya Ozawa, Tokyo (2017)
Wichai Prayoonwiwat, Cheng Mai (2018)
Takanori Teshima, Sapporo (2019)
Yao-Chan Chen, Taipei (2020)
Phu Chi Dong, Ho Chi Min (2021)
Deng Chyang Wu, Kaohsiung (2022)
Shuichi Taniguchi, Fukuoka (2023)
He Huang, Hangzhou (2024)

Past Vice President

Deng Chyang Wu, Kaohsiung
Hee Young Shin, Seoul
Yoichi Takaue, Tokyo

Advisor

Tomomitsu Hotta, Nagoya

Secretary General

Takanori Teshima, Sapporo

Auditor

Keiya Ozawa, Tochigi

Committee Member

Bor-Sheng, Kevin Ko, Taipei
Chung Liang Shih, Taipei
Dinesh Pendharkar, Mumbai
Hee Young Shin, Seoul
Hee-Je Kim, Seoul
Jaeseung Lim, Seoul
Kam Man Hui, Singapore
Kevin Ko, Taipei
Kiyoshi Okada, Osaka
Kyung Ha Ryu, Seoul
Oscar Lee, Taipei
Pham Manh Tuan, Ho Chi Min
Shuichi Taniguchi, Fukuoka
Soo-Jin Choi, Seoul
Suradej Hongeng, Bangkok
Szu-Chun Hsu, Taipei
T. J Hwang, Gwangju
Thai-Yen Ling, Taipei
Udomsak Bunworasate, Bangkok
Xue-Tau Cao, Beijing

ACTO Executive Committee

The ACTO Times
Asian Cellular Therapy Organization

Industry Committee

Kellathur N. Srinivasan, Singapore (Chair)
Antonio Lee, Seoul
Chuanyu Zhang, Shanghai
Hidetoshi Shibuya, Kanazawa
Jaeseung Lim, Seoul
Setsuko Hashimoto, Tokyo
Shing-Mou Lee, Taipei
Soojin Choi, Seoul
Takahito Nakamura, Saitama
Tasnim Ara, Dhaka
Tevadas Thangavelloo, Singapore
Veerapol Khemarangsan, Bangkok
Wann Hsin Chen, Taipei

Regulatory Committee

Yoshiaki Maruyama, Tokyo (Chair)
Ashadul Islam, Dhaka
Chenyan Gao, Beijing
Choi Kyoung Suk, Osan
Chung Liang Shih, Taipei
Huang Yan, Beijing
Kiyoshi Okada, Osaka
Li Xiangyu, Beijing
Lu Jiaqi, Beijing
Maria Christina Galli, Rome
Mei-Chen Huang, Taipei
Morakot Papassiripan, Bangkok
Pei-Chen Lin, Taipei
Piyanan Boonprasent, Bangkok
Rusdy Ghazali Malueka, Yogyakarta
Shamsi, Teheran
Togi Junice Hutadjulu, Jakarta
Yi Chu Lin, Taipei

The ACTO Times Committee

Rita Yen-Hua Huang, Taipei (Editor-in-Chief)
Ferry Sandra, Jakarta
Kai-Yan Liu, Beijing
Kellathur N. Srinivasan, Singapore
Mickey Koh, Singapore
Suradej Hongeng, Bangkok
Yoshiaki Maruyama, Tokyo

Regional Manager

Charles Hasegawa, Bangkok
Katsumi Hosoi, Tokyo
Tae Se Kwon, Seoul
Xu Ping, Suzhou
Yukiyo Suzuki, Tokyo

Past Regulatory Subcommittee Member

Geeta Jotwani, India
Wittawat Viriyabancha, Bangkok

Past Committee Member

Jay Lee, Seoul
Shinji Miyake, Tokyo

Past Industry Committee Member

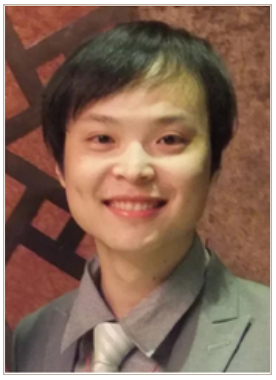
Artit Ungkanont, Bangkok
Kazuto Takesako, Shiga
Kunihiko Suzuki, Tokyo
Hirokazu Takazawa, Beijing

Editorial Board

The ACTO Times
Asian Cellular Therapy Organization

Editorial Office

The ACTO Times
Asian Cellular Therapy Organization



Yung-Che Kuo, PhD
Taipei

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.

Josephine MD, PhD
Yogyakarta

Jojo is a lecturer at the Department of Parasitology, Faculty of Medicine, Public Health, and Nursing at Universitas Gadjah Mada (UGM). Her research interests include dengue infection, parasitology, immunology, and medical education.

Nova, MD, PhD
Yogyakarta

Nova is a faculty member in the Pediatric Surgery Division, Department of Surgery, Universitas Gadjah Mada (UGM), Indonesia. His research interests include stem cell biology, organoid technology, and translational applications of regenerative medicine in pediatric surgery.

D. Renovaldi, M.Sc
Jakarta

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

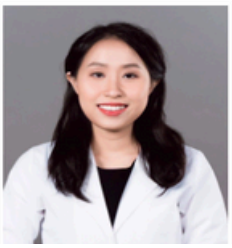
Tony is a PhD student at the Graduate Institute of Pharmacology, National Taiwan University College of Medicine. His research focuses on MSC culture and therapy, specifically exploring their role in regenerative medicine.

Reporters

The ACTO Times
Asian Cellular Therapy Organization

Aghie, PhD
Associate professor
Purwokerto

Mai Huong, PhD
Hanoi



Lucy Pham
MD, PhD
Ho Chi Minh City

Abhi, PhD
India

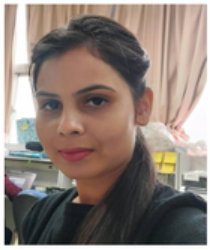
Joseph Cisaka
MD. PhD candidate
Malawi

Gary Kao
PhD candidate
Taipei

Ming-Hao Teng
PhD candidate
Taipei

Edward Law, MS
Hong Kong

Pei-Chi Lan, MS
Taipei



Kajal Singh
PhD candidate
India

Joey, MD, PhD
Hanoi

Dyah Ika R, PhD
Associate Professor
Surabaya

The ACTO Times
Asian Cellular Therapy Organization
2025 NEW YEAR EDITION

CONTENTS

<editor@acto-hq.org> |
<at.chiefeditor@gmail.com>

PROF. AKIHIRO SHIMOSAKA

CHAIRPERSON,
ASIAN CELLULAR THERAPY ORGANIZATION (ACTO)

PROF. HE HUANG

PRESIDENT,
2024 ACTO ANNUAL MEETING

ACTO MEETING SPOTLIGHT 2024

From November 15th to 17th, 2024, the 2024 ACTO meeting was held in Hangzhou, China. Entitled ‘Cellular Therapy and Immunotherapy Conference 2024’, The conference was chaired by Professor Akihiro Shimosaka, the President of Asian Cell Therapy Organization (ACTO), Professor He Huang from the First Affiliated Hospital, School of Medicine, Zhejiang University, Professor Mohamad Mohty from the Sorbonne University and academician of the French Academy of Medical Science and Dr. Dangsheng Li, Chief Editor of the Cell Research. The conference attracted over 150 clinical experts, basic research scientists, young scholars, and representatives from leading biomedical industry enterprises from around the world and approximately 800 participants. Being held in the beautiful historical city of Hangzhou, this is a major global event on hematology and cellular immunotherapy which not only showcased cutting-edge scientific discoveries but also promoted in-depth interdisciplinary exchanges and cooperation. It also pointed out the core directions for future advancements in cellular therapy, immunotherapy, and hematology research.

Professor He Huang initiated the conference with a fascinating report entitled ‘Novel Cellular Therapy for Hematological Malignant Diseases’. In recent years, CAR-T therapy has achieved remarkable progress in the treatment of hematological tumors. Prof Huang team has innovatively developed a sequential "integrated" regimen combining CD7 CAR-T cell therapy with haploidentical allogeneic hematopoietic stem cell transplantation (HSCT) with conventional chemo-conditioning and GVHD prophylaxis. The research findings were published in the New England Journal of Medicine and has become a world-reknowned distinctive "Hangzhou Protocol." Professor Akihiro Shimosaka, the President of Asian Cellular Therapy Organization (ACTO), conducted a profound summary on the challenges faced by cellular therapy.

Prof Shimosaka called for acceleration of the development of regulations for cell therapy and establishment of a supervisory framework to ensure that patients can receive safer, more effective, and more individualized innovative cellular therapy. At the same time, he expressed his expectation that cell therapy should be included in public medical insurance systems in the future, further enhancing the accessibility and fairness.

Professor Xiaojun Huang from Peking University People's Hospital shared the audience with latest advances on the "Beijing" transplant protocol, which was focused on the unique immune reconstitution pattern of haploidentical HSCT. Professor Mohamad Mohty shared his treatment experiences and the latest research findings targeting the GVHD. At the end of his presentation, he quoted Winston Churchill's famous speech, "Never yield to the apparently overwhelming might of the enemy," to envision a bright future for

The Official Report of 2024 ACTO Annual Meeting, Hangzhou, China

Professor Xiaojun Huang from Peking University People's Hospital shared the audience with latest advances on the "Beijing" transplant protocol, which was focused on the unique immune reconstitution pattern of haploidentical HSCT. Professor Mohamad Mohty shared his treatment experiences and the latest research findings targeting the GVHD. At the end of his presentation, he quoted Winston Churchill's famous speech, "Never yield to the apparently overwhelming might of the enemy," to envision a bright future for overcoming GVHD.

He encouraged doctors to believe in their professional expertise, embrace challenges, and actively continue exploring and optimizing treatment options. Professor Anna Sureda, the President of the European Society for Blood and Marrow Transplantation (EBMT), presented a report on the application of CAR-T therapy and biologics in diffuse large B-cell lymphoma (DLBCL) based on European patient data. Professor Zhao Weili, Vice President of Ruijin Hospital, Shanghai Jiao Tong University, delivered a report sharing Ruijin Hospital's exploration experiences in the field of lymphoma immunotherapy, ranging from basic research to clinical practice.

PROF. XIAOJUN HUANG
PEKING UNIVERSITY, CHINA

DR. MOHAMMAD MOHTY
SORBONNE UNIVERSITY, FRANCE

Many world-leading clinical experts and basic research experts including Professor Leo Luznik from Baylor College of Medicine in the USA, Professor Li Tang from École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, Professor Huji Xu from Naval Medical University, and Professor Jianxiang Wang from Peking Union Medical College Institute of Hematology gave insightful reports with cutting-edge results on cellular and immunotherapy.

During the roundtable discussion the top experts in the field focused on the theme of cellular and immunotherapy with an international perspective. The experts expressed their hope to break down barriers in academic research, clinical translation, policy regulations, and other aspects, deepen cooperation and exchanges.

The conference concluded in a warm and friendly atmosphere. During the closing ceremony, the conference presidents highly praised the successful organization of the conference and expressed their gratitude to the colleagues from ACTO, Zhejiang University, IACH, Cell Research, The First Affiliated Hospital of Zhejiang University, Liangzhu Laboratory, and other institutions for their unity and collaboration in making the event a success.
With continuous efforts from everyone, the field of immunotherapy will undoubtedly continue to develop in a more precise, effective, and personalized direction, benefiting patients globally.

Summary Report of the 15th ACTO Meeting Plenary Session

By the Editorial Office of the ACTO Times

Cell Therapy and Gene Therapy - Summary Report

This collection of cutting-edge research highlights transformative advancements in cell therapy and gene therapy, showcasing novel approaches for the treatment of cancer, chronic kidney disease, Charcot-Marie-Tooth disease, and other complex conditions. The studies, conducted by distinguished researchers, underscore the promising potential of these therapies in improving patient outcomes.

Long-Term Follow-Up of BCMA CAR-T Cell Therapy in Relapsed/Refractory Multiple Myeloma Patients.

Prof. Yongxian Hu's study delves into the long-term effects of BCMA Chimeric Antigen Receptor (CAR) T-cell therapy in patients with relapsed or refractory multiple myeloma. A cohort of 141 patients was assessed, with findings demonstrating an impressive objective response rate (ORR) of 94.8%. Significant survival benefits were observed, particularly in patients who underwent prior stem cell transplantation. The study also investigates immunophenotype dynamics and identifies prior stem cell transplants as a crucial factor in enhancing treatment response. These findings highlight the substantial promise of BCMA CAR-T therapies in managing advanced multiple myeloma.

A Clinical Trial of Kidney Regenerative Therapy for Chronic Progressive Kidney Disease.

Dr. Takayasu Ohtake's clinical trial represents an innovative approach to treating chronic progressive kidney disease (CKD) using autologous granulocyte colony-stimulating factor (G-CSF)-mobilized CD34+ cells. In a study of four patients with stage G3b and G4 CKD, the results revealed significant improvements in kidney function and a favorable safety profile. The patients showed enhanced glomerular filtration rates and reduced progression of the disease following the infusion of CD34+ cells, suggesting a novel regenerative treatment strategy for CKD. Notably, transient fever and joint pain were the only observed adverse effects, underscoring the promising potential of cellular therapies in kidney regeneration.

iPSC-Derived Next-Generation T Cell Therapy for Virus-Associated Refractory Tumors

In his pioneering research, Dr. Miki Ando investigates the potential of iPSC-derived T cells to target virus-associated refractory tumors, including those caused by Epstein-Barr Virus (EBV). This innovative study focuses on the development of rejuvenated T cells (rejTs) derived from induced pluripotent stem cells (iPSCs), which exhibit enhanced tumor-killing activity and avoid T-cell exhaustion. The work demonstrates that these HLA-edited

T-cells, produced via CRISPR/Cas9 technology, could revolutionize the treatment of EBV-related malignancies. The study paves the way for the development of off-the-shelf T-cell therapies that could offer a sustainable and scalable solution to treating viral-associated cancers.

Recent Developments in Gene Therapy Focusing on CAR-T Cell Therapy.

Dr. Keiya Ozawa's report highlights the expanding role of gene therapy in the treatment of B-cell malignancies, with a particular emphasis on CAR-T cell therapy. While CAR-T therapies have already shown remarkable success in treating various cancers, the report underscores the need for continued refinement, particularly in improving long-term efficacy and managing T-cell proliferation. Dr. Ozawa introduces an innovative strategy involving a selective regulatory gene (SRG) to control CAR-T cell activity and enhance the safety profile of these therapies. This advancement promises to mitigate risks while improving the therapeutic outcomes of CAR-T cell treatments.

Phase 1 Clinical Study of Cell Therapy with CLZ-2002 for Charcot-Marie-Tooth Disease

Dr. Jaeseung Lim's research explores the potential of CLZ-2002, a cell therapy for Charcot-Marie-Tooth disease (CMT), a rare genetic disorder affecting peripheral nerves. In a Phase 1 clinical trial involving nine CMT patients, the results indicated that CLZ-2002, derived from TMSC (Tonsillar-Mesenchymal Stem Cells) and administered intramuscularly, significantly improved muscle function and nerve conduction. The therapy was well-tolerated, with no severe adverse events. This study marks a critical step forward in regenerative medicine for neurodegenerative diseases, highlighting the role of cellular therapies in addressing unmet medical needs in CMT patients.

This report emphasizes the groundbreaking nature of these studies, demonstrating the potential of cell and gene therapies in transforming the treatment of various - challenging diseases. Each study contributes to the growing body of evidence supporting the use of personalized and regenerative treatments to improve patient health and outcomes across different medical disciplines.

Immunotherapy and Biomarker Discovery - Summary Report

This category presents groundbreaking research on immune therapies and biomarker discovery, focusing on novel therapeutic strategies and identifying key immune signatures that can inform treatment approaches for autoimmune diseases and cancer.

Immune Signatures Guiding the Treatment of Acute Graft-versus-Host Disease (aGVHD)

Dr. Willem Fibbe's study explores the immune signatures that can guide the treatment of acute graft-versus-host disease (aGVHD), a life-threatening complication of allogeneic hematopoietic stem cell transplantation. The research highlights how immune profiling, using mass cytometry (CyTOF) and lymphoid and myeloid cell analysis, can aid in distinguishing patients who are likely to respond to specific treatments, including Mesenchymal Stromal Cells (MSC). The findings suggest that distinct immune cell populations and T-cell markers, such as TCRγδ+ cells, can be associated with aGVHD severity and response to MSC therapy. This work underscores the potential of immune signatures to tailor immunosuppressive treatments, thereby optimizing therapeutic strategies for aGVHD.

Finding Novel Biomarkers in Urothelial Bladder Cancer using Immunoproteomics

In this research, Prof. Abbas Ghaderi investigates the use of immunoproteomics to identify novel biomarkers in urothelial bladder cancer (UBC). The study utilizes the newly established JAM-ICR cell line, which exhibits resistance to chemotherapy and epithelial-mesenchymal transition (EMT) markers, to identify proteins that may be potential biomarkers for UBC progression. The results indicate that muscle-

invasive UBC patients show overexpression of several key proteins, including ENO1, VDAC2, and AKR1B1, while non-muscle invasive patients show distinct biomarkers such as SDF2L1. Additionally, specific heat shock proteins and proteasome activators were also detected in patients at advanced stages, reinforcing their potential as diagnostic and prognostic markers. These findings provide a foundation for future diagnostic tools and therapeutic strategies targeting UBC.

Exosomes and mRNA as Novel Cancer Therapies

Dr. H. Kim Lyerly's presentation explores the potential of exosomes and mRNA as novel therapeutic and diagnostic tools in cancer treatment. This research delves into the biogenesis of exosomes, their role in antigen delivery, and their potential as cancer vaccines. The presentation also covers the latest developments in mRNA technologies, including the use of mRNA for vaccines, antigen delivery, and as self-replicating RNA. Through a discussion of Good Manufacturing Process (GMP) standards and clinical applications, Dr. Lyerly outlines how exosome and mRNA-based therapies could revolutionize cancer treatment and offer new avenues for personalized therapeutic interventions.

This summary demonstrates the innovative potential of immunotherapy and biomarker discovery in advancing precision medicine. The research not only enhances our understanding of immune mechanisms in disease but also paves the way for developing personalized therapeutic strategies and improving patient outcomes.

CGT Regulatory Framework - Summary Report

This category focuses on the regulatory landscape for the approval and market introduction of advanced therapies and regenerative medicine. It also addresses the global efforts to streamline approval processes and ensure the safety and efficacy of innovative treatments.

European Regulatory Framework for Advanced Therapy Medicinal Products: An Updated Overview

Dr. Maria Cristina Galli outlines the evolving regulatory framework for Advanced Therapy Medicinal Products (ATMPs) in Europe. The presentation emphasizes how European Medicines Agency (EMA) and national regulatory authorities have tailored procedures for clinical trials and market approval. The focus is on fostering the progress of gene and cell therapies, with the aim of ensuring that safe and effective ATMPs are delivered to patients. Recent updates to the European Pharmacopoeia's guidelines are designed to maintain high standards in ATMP production, promoting the transition of these therapies from the bench to the bedside.

Regulatory Update for Regenerative Medicine in Japan

Dr. Shinichi Noda presents Japan's regulatory approach to regenerative medicine, particularly after the implementation of the "Act on the Safety of Regenerative Medicine" and the "Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act" in 2014. These regulations have streamlined the approval process for regenerative therapies, offering conditional and time-limited approvals for innovative treatments. Japan has granted full approval for several regenerative products, positioning itself as a global leader in regenerative medicine. Noda emphasizes ongoing efforts to further improve regulatory efficiency and safety standards for regenerative products.

15th ACTO Meeting Plenary Session Summary Report

Thailand's Perspective on ATMP: Regulator Role by Thai FDA

Dr. Morakot Papassiripan provides a detailed overview of the Thai FDA's regulatory role in advancing the introduction of Advanced Therapy Medicinal Products (ATMPs) into the market. His discussion focuses on enhancing the efficiency of the ATMP approval process, including streamlining approval steps and incorporating digital technologies for documentation and tracking. The Thai FDA is working on establishing a specialized team for ATMPs to support their development and market launch. Key recommendations also include setting international standards for ATMP safety and efficacy, supporting research, and fostering international collaboration to boost the ATMP market.

This refined summary provides a clear overview of the regulatory frameworks and the efforts being made to ensure the safe and effective delivery of novel therapies to patients. These regulatory updates are crucial for promoting the development and market introduction of advanced therapeutics, supporting global access to innovative treatments.

Welcome from Singapore

2025 ACTO Annual Meeting will be held this August!

The landscape for Cell and Gene Therapy continues to move at a bewilderingly and astonishingly rapid pace worldwide. Asia is no exception and together with the USA, China has set the pace for the CAR-T revolution. Japan has also revolutionised the field with the discovery of induced pluripotent stem cells (IPSC) and we have seen exciting innovations happening in India and other regions. In fact, almost all countries I have been in contact with are pursuing a national interest in cell and gene therapy.

The promise as well as the challenges for this field are enormous with ramifications not only to the biomedical sector as well as a growing role driving economic growth as well as transforming the treatment algorithms for a whole range of diseases from haematology to degenerative disorders.

We would therefore like to welcome everyone to the next ACTO Congress which will be held in Singapore from 14th to 16th August 2025. This promises to be an ambitious meeting with a program that will cover all aspects important to cell and gene therapy as mentioned above. The program will serve to update attendees on the latest scientific initiatives in the Asia Pacific region as well as the unique opportunities and challenges of this region.

In addition, the congress will also focus on the rising cost of such therapies, affordability and equity of access issues as well as the critical regulatory infrastructure that needs to accompany this field by providing the governance and quality framework.

PROFESSOR MICKEY B C KOH

CONSULTANT HAEMATOLOGIST & DIRECTOR OF THE STEM CELL TRANSPLANTATION PROGRAMME
ST. GEORGE'S HOSPITAL

ACTO Vice President (SIngapore)

Professor Mickey Koh received his medical degree at the National University of Singapore followed by all of his subsequent specialist Haematology training (FRCPath, MRCP and PhD) in London.

He holds several joint positions. Prof Koh is the Clinical Director of the Haematology, Renal and Oncology Departments at St George's University Hospital, London, UK and part of Infection and Immunity Academic Group at St George's Medical School.
He was until recently also the Programme and Medical Director of the Academic Cell and Gene Therapy Facility in Singapore involved in cell therapy trials across haemato-oncology and regenerative medicine.

Professor Mickey Koh has been appointed as part of the Expert Advisory Panel at the World Health Organisation and sits on the Expert Committee on Biological Standardisation.
He is the current Vice-President of the Worldwide Network for Blood and Marrow Transplantation (WBMT) and a past Board member of the International Society of Cellular Therapy (ISCT). He is also on the Board of Directors for ISBT and ICCBBA, an international organisation overseeing the standard for terminology, coding and labelling of medical products of human origin.

Welcome from Singapore

The focus on ethical, legal and regulatory issues is critical with the continued unproven use of cell and gene therapy, particularly in the field of stem cells and its promise of tissue regeneration.
The congress will provide a forum for discussion and knowledge exchange on cell and gene therapy manufacturing capabilities, both locally and nationally. It will also discuss the pressing need for specialist manpower and the requisite training involved. In addition, we will also focus on the patient perspective and how disease treatment is being revolutionised by this exciting area of cell and gene therapy.
So, I urge everyone who is interested in this field and those who would want to know more about developments in Singapore and the Asia-Pacific region to register and attend this congress.

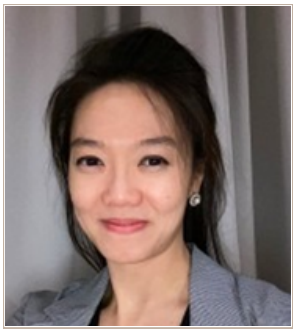
Singapore is a compact city that has always been receptive to new technologies and advances. It has an excellent infrastructure to host scientific congresses while also allowing attendees the opportunities to explore the multi-cultural, technologically advanced city state that it is known for and the wealth of interesting tourist attractions to explore.

Please mark your calendar and come join us August 14-16th!

Professor Mickey B C KOH
Together with congress co-organizers Dr. Francesca Lim and Dr. Srinivasan Kellathur
Singapore

DR SRINIVASAN KELLATHUR

DIRECTOR OF ADVANCED THERAPY PRODUCTS BRANCH
SINGAPORE HEALTH SCIENCES AUTHORITY



DR FRANCESCA LIM

SENIOR CONSULTANT HEMATOLOGIST
SINGAPORE GENERAL HOSPITAL

IMAGE FROM CANVA.COM

Cynthia Retna Sartika, Rima Haifa, Angliana Chouw
Faculty of Pharmacy, Universitas Padjajaran, Indonesia
PT Prodia Stem Cell Indonesia, Indonesia

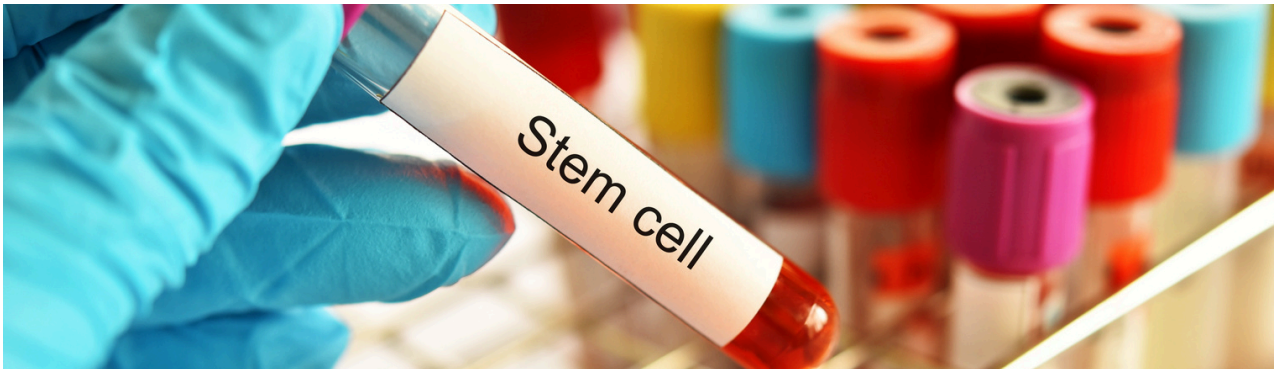


IMAGE FROM CANVA.COM

Challenges and Opportunities in Regulation of Stem Cells, Cells, and Their Derivatives Applications in Indonesia

Introduction

Stem cell, cell and their derivatives has emerged as a promising treatment modality for a spectrum of diseases, particularly degenerative disorders. The remarkable regenerative potential of stem cells lies in their capacity to secrete various molecular mediators, encompassing anti-apoptotic, immunomodulatory, angiogenic, and chemoattractant abilities, thereby facilitating tissue repair (Han et al., 2022). Beyond their broad use in basic research, stem cells, cells and their derivatives have many more applications in modern healthcare and have opportunities to be developed into innovative treatment strategies. Nevertheless, stem cell, cells and their derivatives therapy are not only a novel medical practice but as well as an Advanced Therapy Medicinal Products (ATMP). Regulation performs a pivotal position in directing the development and clinical applications of Stem cell, cell and their derivatives. This regulatory framework serves as a basis and offers an organized and comprehensive pathway for the research, improvement, and clinical implementation. Some countries have begun to consider stem cells, cells and their derivatives as a form of organic or medicinal product and set up guidelines to navigate the complicated terrain of their development. These guidelines no longer only embody the scientific and technical aspects of stem cell, cell and their derivatives therapy but also address ethical considerations, patient safety, and the overall societal impact of these advanced therapies. The following regions consisting of America, Canada, Japan, and Korea, have accredited and used various types of stem cells in clinical settings. Worldwide, several products are currently the subject of ongoing investigations (Chen et al., 2017).

In Indonesia, the Ministry of Health (MoH) and Indonesian Food and Drug Authority (FDA)/Badan Pengawas Obat dan Makanan (BPOM) have not yet approved any stem cell, cell and their derivatives products for marketing authorization. However, they developed several guidelines following international standards including the guidelines of the World Health Organization (WHO), United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), and the International Conference on Harmonization (ICH). The MoH regulates the implementation of therapy, while the Indonesian FDA oversees matters related to the products. Moreover, as Indonesia is one of the largest country with Muslim population, the issue of Halal is also an important subject to discus.

This article summarizes the stem cell, cell and their derivatives regulation in Indonesia made by the Indonesian MoH and the Indonesian FDA and looks to discuss further challenges and advancements of stem cells, cells, and their derivatives in Indonesia. Moving beyond a mere exploration of regulation, the article strives to enrich the regulation perspective in -

Indonesia concerning both stem cell, cell and their derivatives therapy and emerging innovative products.

Stem Cells, Cells, and Their Derivatives Potency, Research and Clinical Applications in Indonesia

Since the discovery of stem cells, researchers have identified different populations of stem cells in various organs with diverse functions that possess the unique ability to self-renew and differentiate into various cell types. This capability renders them potentially applicable in disease therapy. Stem cells also serve as immunomodulatory agents, capable of ameliorating conditions with compromised immune systems. These roles make stem cells highly promising and have transformed the field of cell biology into a rapidly advancing domain (Vizoso et al., 2017)

Another innovative product derived from stem cells is the secretome. t consists of bioactive molecules produced by cells within the extracellular space (Ibrahim & Allam, 2022).

The secretome includes (1) soluble components like cytokines, chemokines, immunomodulatory molecules, and growth factors, and (2) extracellular vesicles like microvesicles and exosomes, which help cells communicate by delivering microRNA and proteins. The secretome additionally performs an equal function to stem cells or cells in regenerative therapy. Despite its identified potential, the manufacturing processes for both stem cells and secretome, stay limited to the local laboratory bench scale as there is still lack of marketing authorization regulation is still develop by the regulators.

In Indonesia, currently, there is no cell-based medicine product or stem cell that has marketing authorization from the Indonesian FDA. However, numerous clinical studies related to cellular applications are ongoing, and the number of applications continues to increase rapidly. Stem cell research in Indonesia is advancing more rapidly compared to other types of cell therapy. Consequently, research related to cell therapy in the country is predominantly focused on stem cells and their derivatives (Table 1).

No	Title	NCT Number	Study Start (Actual)	Status	Conditions	Interventions	Locations
1	Stem Cell in Acute Myocardial Infarction	NCT04340609	2019	Completed	Acute Myocardial Infarction	Biological: Mesenchymal Stem Cells	PT Prodia StemCell Indonesia, Jakarta, Indonesia Medistra Hospital, Jakarta, Indonesia
2	The Effects of Mesenchymal Stem Cell Secretome in Rheumatoid Arthritis Patients	NCT05925647	2022	Completed	Rheumatoid Arthritis	Drug: Mesenchymal stem cell secretome Drug: Placebo	Moewardi General Hospital, Surakarta, Middle Java, Indonesia
3	Mesenchymal Stem Cell Therapy (MSCs) and Conditioned Medium Therapy for Osteoarthritis	NCT04314661	2020	Unknown status	Osteoarthritis, Knee	Biological: Arthroscopy with Mesenchymal Stem Cells + Secretome + Secretome Biological: Arthroscopy with Secretome + Mesenchymal Stem Cells + Secretome Biological: Non Arthroscopy with Mesenchymal Stem Cells + Secretome + Secretome 1 more	Gatot Soebroto Hospital, Jakarta Pusat, DKI Jakarta, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
4	Stem Cell and Conditioned Medium for Cerebral Palsy	NCT04314687	2021	Unknown status	Cerebral Palsy	Biological: Umbilical Cord Mesenchymal Stem Cells Biological: Conditioned Medium Other: Standard Therapy	Indonesian National Brain Center, Jakarta, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
5	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients	NCT04535856	2020	Completed	Covid19 CoronaVirus Infection SAR	Drug: allogeneic mesenchymal stem cell Other: Placebo	Site 550: University of Hasanuddin/ Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia
6	Combination of Conditioned Medium and Umbilical Cord-Mesenchymal Stem Cells Therapy for Acute Stroke Infarct	NCT05008588	2022	Unknown status	Ischemic Stroke	Biological: Conditioned Medium Biological: Umbilical Cord Mesenchymal Stem Cells Procedure: Neurologic and Neurotrophic Drugs	Gatot Soebroto Hospital, Jakarta Pusat, DKI Jakarta, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
7	Umbilical Cord Mesenchymal Stem Cell Improve Cardiac Function on ST-elevation Myocardial Infarction (STEMI) Patients	NCT05935423	2023	Not yet recruiting	ST Elevation Myocardial Infarction	Biological: Umbilical Cord Mesenchymal Stem Cell transplantation	Cipto Mangunkusumo Hospital, Jakarta Pusat, DKI Jakarta, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
8	Umbilical Cord Mesenchymal Stem Cell for Liver Cirrhosis Patient Caused by Hepatitis B	NCT04357600	2018	Unkown status	Liver Cirrhosis	Biological: Allogeneic Umbilical Cord Mesenchymal Stem Cell	Cipto Mangunkusumo hospital, Jakarta, DKI Jakarta, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
9	Hair Regeneration in Androgenetic Alopecia	NCT06066827	2023	Active, not recruiting	Androgenetic Alopecia	Drug: Minoxidil Topical Other: Secretome from adipose-derived stem cells Combination Product: Combination of minoxidil and secretome from adipose-derived stem cells	RSUP Nasional Cipto Mangunkusumo, Jakarta Pusat, DKI Jakarta, Indonesia Universitas Indonesia, Jakarta Pusat, Jakarta, Indonesia
10	The Effects of Mesenchymal Stem Cell Secretome in Lupus Patients	NCT05921058	2022	Completed	Lupus Erythematosus	Drug: Secretome Drug: Placebo	Moewardi General Hospital, Surakarta, Middle Java, Indonesia
11	Comparison of Keloid Volume and Symptoms Reduction Between Intralesional Umbilical-Cord Mesenchymal Stem Cells, Its Conditioned Medium, and Triamcinolone Acetonide Injection as Keloid Therapy: A Randomised Controlled Trial	NCT05887804	2021	Completed	Keloid Stem Cell	Biological: umbilical cord-derived mesenchymal stem cells (UC-MSC) Biological: umbilical cord-derived mesenchymal stem cells conditioned medium (UC-CM) Drug: Triamcinolone Acetonide (TA)	RSPAD Gatot Soebroto, Jakarta Pusat, DKI Jakarta, Indonesia
12	The Effect of Intralesian Injection of Umbilical Cord Mesenchymal Stem Cells, Its Conditioned Medium, and Triamcinolone Acetonide on Type 1:3 Collagen Ratio and Interleukin-10 Levels in Keloid: A Randomised Controlled Trial	NCT05939817	2021	Completed	Keloid Stem Cell	Biological: umbilical cord-derived mesenchymal stem cells (UC-MSC) Biological: umbilical cord-derived mesenchymal stem cells conditioned medium (UC-CM) Drug: Triamcinolone Acetonide (TA)	RSPAD Gatot Soebroto, Jakarta Pusat, DKI Jakarta, Indonesia
13	Long-term Safety of UC-MSC Transplantation in Patients With Retinitis Pigmentosa	NCT05786287	2023	Enrolling by invitation	Retinitis Pigmentosa	Biological: Conditioned Medium (CM) Biological: Umbilical Cord Mesenchymal Stem Cell (UC-MSC)	Jakarta Eye Center Hospital, Jakarta, DKI Jakarta, Indonesia Sardjito Hospital, Yogyakarta, Special Region, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
14	Safety Issues of Peribulbar Injection of UC-MSC in Patients With Retinitis Pigmentosa	NCT04315025	2018	Completed	Retinitis Pigmentosa	Biological: Umbilical Cord Mesenchymal Stem Cell (UC-MSC) Biological: Conditioned Medium (CM)	Jakarta Eye Center Hospital, Jakarta, DKI Jakarta, Indonesia Sardjito Hospital, Yogyakarta, Special Region, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
15	Mesenchymal Stem Cell Secretome In Severe Cases of COVID-19	NCT05122234	2020	Completed	COVID-19	Biological: Injection of secretome - mesenchymal stem cell Other: Placebo Drug: Standard treatment of Covid-19	RSUPN Dr. Cipto Mangunkusumo, Jakarta Pusat, DKI Jakarta, Indonesia RSUP Fatmawati, Jakarta, DKI Jakarta, Indonesia RSUP Persahabatan, Jakarta, DKI Jakarta, Indonesia Rumah Sakit Universitas Indonesia, Depok, Jawa Barat, Indonesia
16	Biological Skin Graft with Keratinocyte-stem Cell Co-culture for Burn Patients	NCT05652816	2022	Recruiting Berubah jadi unknown status	Burn Degree Second Burn Degree Third	Procedure: Split-thickness skin graft Biological: Artificial skin graft Biological: Artificial skin graft co-culture	RSUPN Cipto Mangunkusumo, Jakarta Pusat, DKI Jakarta, Indonesia
17	Adipose-derived Stem Cell Conditioned Media as a Novel Approach for Hair Regrowth in Male Androgenetic Alopecia	NCT05296863	2021	Completed	Alopecia, Androgenetic Hair Loss/Baldness	Combination Product: Non-concentrated adipose-derived stem cell conditioned media and 5% Minoxidil Combination Product: Concentrated adipose-derived stem cell conditioned media and 5% Minoxidil Combination Product: Placebo and 5% Minoxidil	Universitas Indonesia, Jakarta Pusat, Jakarta, Indonesia
18	Role of UC-MSC and CM to Inhibit Vision Loss in Retinitis Pigmentosa Phase I/II	NCT05909488	2023	Recruiting	Retinitis Pigmentosa	Biological: 1.5 x 10^6 UC-MSC + CM Biological: 5 x 10^6 UC-MSC + CM	RSUP Dr. Sardjito, Yogyakarta, DI Yogyakarta, Indonesia PT Prodia StemCell Indonesia, Jakarta, Indonesia
19	Stem Cells and Secretomes for Infertility Therapy in Polycystic Ovary Syndrome (PCOS) Patients With Insulin Resistance	NCT05279768	2022	Recruiting Berubah jadi unknown status	Polycystic Ovary Syndrome	Biological: UC-MSCs Biological: Secretomes Biological: UC-MSCs and Secretomes 1 more	PT Prodia StemCell Indonesia, Jakarta, Indonesia RSPAD Gatot Soebroto, Jakarta Pusat, DKI Jakarta, Indonesia
20	Microneedle Versus Fractional CO_2 Laser for Skin Aging Treatment With Stem Cell Secretome in Indonesian Adult Women	NCT05508191	2022	Completed	Skin Aging Transepidermal Water Loss	Device: Fractional CO_2 Laser Device: Microneedle	Faculty of Medicine, Universitas Indonesia, Jakarta Pusat, DKI Jakarta, Indonesia
21	Therapeutic Potential of Stem Cell Conditioned Medium on Chronic Ulcer Wounds	NCT04134676	2019	Completed	Chronic Ulcer	Drug: Conditioned Media	Mayapada Hospital, Tangerang, Banten, Indonesia Indra Clinic, Tangerang, Banten, Indonesia Sukma Clinig, Tangerang, Banten, Indonesia
22	Potential Injection of Human Umbilical Cord Secretome in the Case of Trophic Ulcers (Pre-post Intervention)	NCT05777213	2019	Completed	CM-MSC ; Stem Cell ; Trophic Ulcer ; Leprosy ; Morban Hansen; Secretom	Biological: Secretome	Sukma Clinic, Tangerang, Banten, Indonesia RS Alverno Singkawang, Singkawang, West Borneo, Indonesia
23	Effectiveness of PRP, Conditioned Medium UC-MSCs Secretome and Hyaluronic Acid for the Treatment of Knee Osteoarthritis	NCT05579665	2022	Completed	Knee Osteoarthritis	Biological: Platelet-rich Plasma Biological: Conditioned Medium From Umbilical Cord Mesenchymal Stem Cell Culture (MSCs) Secretome Drug: Low Molecular Weight Hyaluronic Acid	Mohammad Hoesin Central General Hospital\Palembang, Palembang, South Sumatera, Indonesia
24	HyaloFAST Trial for Repair of Articular Cartilage in the Knee	NCT02659215	2015	Active, not recruiting	Defect of Articular Cartilage	Device: Hyalofast Procedure: Microfracture	Medistra Hospital, Jakarta, Indonesia Royal Progress Hospital, Jakarta, Indonesia Physicians Research Group, Tempe, Arizona, United States Axis Clinical Trials, Los Angeles, California, United States (and 44 more…)

Updates on Clinical Trials

25	Effectivity of Allogenic Umbilical Cord Mesenchymal Stem Cells Conditioned Media for Osteoarthritis of the Knee Joint	NCT06688318	2024	Active, not recruiting	Osteoarthritis Knee	Biological: Intra-articular secretome injection therapy	Moewardi General Hospital, Surakarta, Central Java, Indonesia
26	Development of Products Based on Secretom from Stem Cell Conditioned Medium for Melasma Therapy	NCT06516419	2024	Recruiting	Melasma	Drug: Concentrated secretome injection 2mL Drug: Tranexamic acid injection Drug: Triple combination cream	Clinical Research Supporting Unit-Faculty of Medicine, University of Indonesia, Jakarta, Indonesia Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
27	Clinical Utility and Safety of Human Umbilical Cord Mesenchymal Stem Cell Secretome in Moderate Neurocognitive Impairment (Dementia)	NCT06632470	2024	Not yet recruiting	Dementia Moderate Dementia	Drug: Secretome injection Drug: Vitamin B12 injection	Panti Wenda Hana, South Tangerang, Banten, Indonesia
28	Safety and Feasibility of Human Umbilical Cord Mesenchymal Stem Cell-Derived Secretome in the Treatment of Liver Cirrhosis: a Comprehensive Evaluation of Fibrosis Reduction, Immunomodulation, and Hepatic Regeneration: a Single Center, Randomized, Phase I Clinical Trial	NCT06629909	2024	Not yet recruiting	Liver Cirrhosis	Drug: Secretome	Liver Clinic Prof Ali Sulaiman, Jakarta, Indonesia
29	Clinical Utility and Safety of Human Umbilical Cord Mesenchymal Stem Cell Secretome in Drug Resistant Epilepsy Single Center, Non-randomized, Phase I Clinical Trial	NCT06638970	2024	Not yet recruiting	Epilepsy Drugs Resistant Epilepsy	Drug: Secretome	Main Clinic Prof. Dadang Hawari, Jakarta, Indonesia

SOURCE: (CLINICALTRIALS.GOV, N.D.) BY JANUARY 2025

Current Regulatory Framework in Indonesia

The regulatory framework for stem cell, cell and their derivatives in Indonesia is in place. The MoH and the Indonesian FDA play a vital role in regulating stem cell, cell and their derivatives therapies. MoH focuses on healthcare services and research in hospitals, while the Indonesian FDA focuses more on product approval and GMP facility. The MoH established the Stem Cell Committee consisting of experts from the government, academicians, industry, and private sectors. The committee serves as an advisory body for the MoH regarding the regulation of stem cell, cells, and their derivatives, approval for research in healthcare facilities as well as processing facilities.

Indonesian Ministry of Health (MoH)

In 2009, the MOH issued the Minister of Health Regulation Number 36 of 2009 regarding stem cell treatment and updated by Health Law Number 17 of 2023 to addressed the clinical indications for stem cell, cells, and their derivatives therapy, that it must be scientifically proven, intended for health restoration, prohibited for reproductive use, and not derived from embryonic cells. The regulations are also detailed in MoH Regulation Number 833 and 834 of 2009 (Guidelines for the Implementation of Stem Cell Medical Services).

In 2012, for assessment of operational permit for stem celll laboratory, the MoH release the Minister of Health Regulation Number 48 of 2012 (Implementation of Cord Blood Stem Cell Bank) and Minister of Health Regulation Number 50 of 2012 (Implementation of Stem Cell Processing Laboratory for Clinical Application).

Regulations related to the provision of stem cell, cells, and their derivatives are governed by Minister of Health Regulation Number 32 of 2018 which concerns the implementation of stem cell, cells, and their derivatives therapy services. This regulation for stem cell therapy mandates that only non-embryonic adult stem cells can be used for treatment. These stem cells can be sourced from the umbilical cord of newborns, bone marrow, peripheral blood, and other similar sources. The use of embryonic stem cells raises ethical questions regarding the moral status of embryo, thus its clinical application is forbidden within Indonesia. In this regulation, the use of stem cell, cells, and their derivatives is divided into two schemes: research-based therapy and standardized therapy.

Research-based therapy is where the therapeutic application of stem cells and/or cell therapy is conducted on patients as research subjects to assess their safety and efficacy of stem cells and/or cell therapy. On the other hand, standardized therapy are evidence-based treatments that follow established service standards set by the Ministry of Health (MoH). Additionally, an in-depth discussion is underway regarding the standard facilities for processing and administering stem cells, cells, and their derivatives for therapy. Expanding beyond the regulations governing these facilities, the government is poised to enact further guidelines specifying the diseases eligible for stem cell, cells, and their derivatives therapy and outlining the qualifications required for the medical professionals administering it.

These regulations will take form of standards therapy for stem cell, cells, and their derivatives therapy, developed collaboratively with the collegium. As part of the procedural checks, these documents are subject to approved by

the Minister of Health and meticulous reviewed by the stem cell committee. In 2024, MoH released the Government Regulation Number 28 of 2024 that addresses the Implementation Guidelines for the Health Law including Cell-based Therapies and/or Stem Cells. Moreover, the MoH issued the first approved standardized therapy services through a MoH decree Number 1359 of 2024 on guidelines for the provision of stem cell therapy services in orthopedics and traumatology.

Indonesian FDA/Badan Pengawas Obat dan Makanan (BPOM)

Along with the MoH, the Indonesia FDA (BPOM) regulates the development and usage of stem cell, cells, and their derivatives products. Nevertheless, medications derived from cells are different fundamentally from those based on chemical or natural substances. The main different lies in their sources of active ingredients and mechanisms of action. Cell-based medication typically used living cells or their derivatives, like stem cells or genetically engineered substances. In contrast, chemical-based medicine are made from synthetic compounds, and nature-based medicine originate from natural substances like plants or animals. The mode of action and targets of these medications may vary. Cell-based medications often function by promoting cell regeneration or replacing damaged cells, while chemical or nature-based medications may interact with diverse biochemical processes in the body to achieve therapeutic effects (Mousaei et al, 2022; Mathur & Hoskins, 2017).

In Indonesia, the BPOM classifies stem cells and cell-based treatments as investigational new drugs (IND)/Obat Pengembangan Baru (OPB).. Before a new drug can be marketed in Indonesia, it must go through a long development process, starting from the concept development, development of the active ingredient, manufacturing and analytical testing, non-clinical testing, and lastly the clinical trial to prove the safety, efficacy, and quality . The data from these trials are then used for the marketing authorization registration. BPOM has regulations (BPOM Regulation Number 16 of 2015) for managing and assessment IND. This guidelines provides information related to the management and evaluation of IND. These regulation encompasses procedures and requirements for the registration of IND, covering various aspects, including document requirements and other aspects related to registration process. This guideline covers the role of BPOM in overseeing the IND to obtain marketing authorization.

However, a draft revision of this regulation has emerged, as the provisions regarding the management and assessment of investigational new drug developments as outlined in Indonesian FDA Regulation Number 16 of 2015 are no longer aligned with current legal needs and the advancements in science and technology in the pharmaceutical field, necessitating its replacement. In connection with this, the Indonesian FDA issued letters to several stem cell, cells, and their derivatives company in Indonesia, requesting input on the draft revision. Despite these efforts, it was found there are several challenges in the draft revision because of the unique characteristics of stem cells, which differ significantly from conventional drugs.[PS1]

BPOM issued Regulation Number 24 of 2017, which outline the criteria and procedures for drug registration in Indonesia. This regulation sets the requirements drug manufacturers must meet when registering a product. For stem cells, cells, and their derivatives products, Regulation Number 18 of 2020 (Guidelines for the Assessment of Human Cell-Based Drugs) also applies. The regulation requires that production facilities for stem cells and their derivatives have a Cara Pembuatan Obat yang Baik (CPOB) certification, confirming the facility follows Good Manufacturing Practices (GMP). BPOM also mandates that manufacturers provide detailed documentation on their processes, including the quality attributes, raw materials, and specifications of the cells and their derivatives, to ensure product quality for clinical use (Chouw et al., 2021). Additionally, manufacturers must describe how the active substances and finished products are made, including the specific processes involved in cell manipulation and how the cells' physiological functions are maintained.

Halal Certification

Apart from that, the Halal certification is also a key issue related to cell therapy. In Indonesia, these regulations are regulated in Presidential Regulation of the Republic of Indonesia No. 6 of 2023, as well as Fatwa of the Indonesian

Ulama Council/Majelis Ulama Indonesia (MUI) No. 51 of 2020 and No. 1 of 2020. The Fatwa MUI No. 51 of 2020 provides standards use of stem cell, cells, and their derivatives in medical therapy in Indonesia. The use of stem cells, cells, and their derivatives is allowed in Indonesia under specific conditions, particularly when there is a Sharia requirement, such as for disease treatment, reconstructive therapy, and medical research. Presidential Regulation of the Republic of Indonesia No. 6 of 2023 regulates Halal Certification for Medicines, Biological Products, and Medical Devices, including stem cells. This regulation outlines the procedures for obtaining halal certification, ensuring that these products meet the halal criteria in terms of raw materials, additives, production processes, storage, packaging, and distribution. For stem cells, this means they must originate from halal sources and be processed according to Sharia principles, with strict limits on the use of forbidden (haram) substances during isolation, cultivation, or processing. The certification process is overseen by a Halal Inspection Agency/Lembaga Pemeriksa Halal (LPH) which works under the Halal Product Assurance Organizing Agency/Badan Penyelenggara Jaminan Produk Halal (BPJPH) to issue halal certificates after testing and examination. The production of stem cell, cells, and their derivatives products must comply with halal manufacturing practices and use only halal materials.

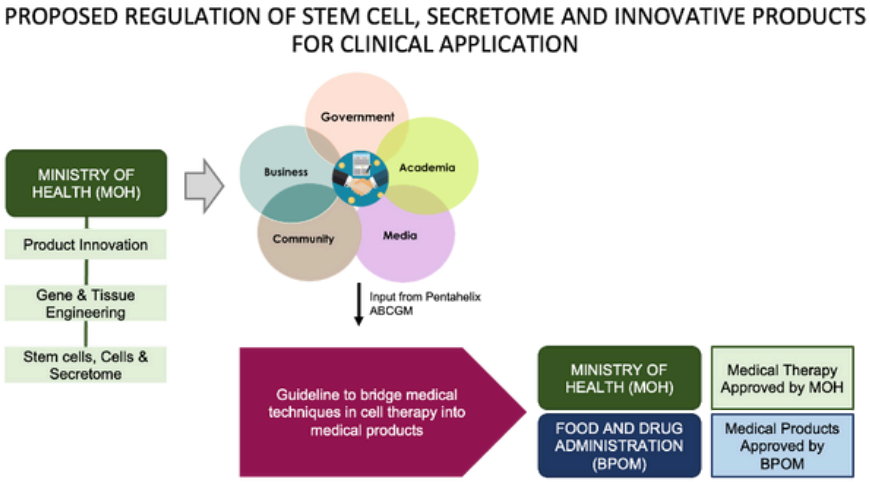
Challenges in Stem Cell, Cells, and Their Derivatives Research and Clinical Applications

While Indonesia has established several regulations and guidelines stem cell, cells, and their derivatives therapy, there are still unresolved gaps and challenges. One issue is the lack of clear definitions in some regulatory frameworks, such as in Ministry of Health (MoH) Regulation No. 32 of 2018 on the certification of expert personnel, which leaves ambiguity about its technical implementation. This can limit healthcare providers' ability to offer stem cell therapies to patients who could benefit from them (Salam, 2023). To address this, organizations like the Indonesian Stem Cell Association/Asosiasi Sel Punca Indonesia (ASPI) and the Indonesian Association of Tissue Engineering and Cell Therapy/Perhimpunan Dokter Seminat Rekayasa Jaringan dan Terapi Sel Indonesia (REJASELINDO) can support the Stem Cell Committee by offering training and certification for scientists and physicians in this field.

Another challenge is related to where stem cell therapy can be carried out. Research-based therapy must be conducted in government-approved teaching hospitals, their collaborating hospitals, or private hospitals with government permits. These hospitals need teams of qualified medical professionals and standardized facilities to carry out stem cell treatments, as outlined in MoH Regulation No. 32 of 2018. However, many hospitals may not be prepared or equipped fully and the established facilites tends to work independently and are less likely to collaborate, limiting patient access to these therapies.

Moreover, translating stem cell research from the laboratory to clinical applications is another challenge. It requires extensive preclinical testing, large-scale clinical trials, and regulatory approval to demonstrate safety and efficacy, all of which are costly. In the United States, for example, preclinical data requirements can be relaxed for certain disease models, as long as safety and ethical concerns are addressed in clinical trials (George, 2011). In Indonesia, improving coordination among stakeholders—academia, business, community, and government (ABCG)—is essential to overcome these barriers.

Additionally, the complexity of stem cell production further limits distribution. Indonesia's archipelagic geography makes it difficult to distribute therapy supplies across the country. The dosage, packaging, and method of administration are critical to the effectiveness of stem cell treatments, even though the production steps are standardized. This makes stem cell therapies more complex and time-consuming to develop compared to traditional chemical drugs, delaying their availability and increasing the cost. Despite this, four Indonesian facilities—PT Prodia StemCell Indonesia, PT Bifarma Adiluhung, Daewoong Biologics Indonesia, and Kimia Farma—have obtained Good Manufacturing Practice (GMP) accreditation, ensuring high product quality and helping facilitate nationwide distribution.



Future Direction

Currently, the Stem Cell Committee of the Ministry of Health, in collaboration with medical specialists from the College of Medicine, is working on creating standard guidelines for specific diseases under Health Law Number 17 of 2023. These standards will be based on evidence-based data to ensure patient safety during stem cell, cells, and their derivatives therapies. The standard guidelines also emphasize that stem cell, cells, and their derivatives research and therapy require collaboration, scientific knowledge, and resource sharing through the concept of the ABCGM Penta helix: Academic, Business, Clinician/Collegium, Government and Media. This approach aligns with the broader vision of the Indonesian Stem Cell Consortium, as illustrated in Figure 1 (MoH, 2013). Each sector within the Penta helix has a specific role in driving the advancement of stem cell, cells, and their derivatives therapy, offering great promise for treatment and establishing Indonesia as a leader in providing stem cell, cells, and their derivatives therapy services. For example, the approval scheme for stem cell, cells, and their derivatives therapies can be divided according to the category such as medical procedure (approved by MOH) or product (approved by the Indonesian FDA). These categories will be based on recommendations from experts in the Penta helix groups, ensuring a comprehensive and coordinated approach to the development and regulation of stem cell, cells, and their derivatives therapies.

In the future, stem cell, cells, and their derivatives therapy could become a major part of medical tourism in Indonesia. To make this possible, the government, research institutions, and industry stakeholders need to collaborate through funding, policy frameworks, and strategic partnerships to support stem cell, cells, and their derivatives research and therapy in Indonesia. Key factors like facilities, equipment, and funding are essential for advancing this field, but laboratories often require substantial budgets, making investment in sustainable funding models a significant challenge. In Indonesia, the National Research and Innovation Agency, often referred to as Badan Riset dan Inovasi Nasional (BRIN) plays a role in addressing this by providing funding and grants to accelerate collaborative research.

Expanding public funding and insurance coverage for stem cell, cells, and their derivatives therapy would also improve access for patients. Adequate funding from both public and private sectors is necessary to drive research and clinical applications. Additionally, fostering interdisciplinary collaboration and educational programs that bridge the gap between basic science, clinical practice, and industry will help build a skilled workforce and promote knowledge transfer. Hospitals and laboratories can collaborate on training programs and workshops, certified by the Ministry of Health (MoH), to ensure that doctors and scientists are properly trained to perform the therapy.

The Indonesian FDA can support manufacturing labs in meeting the necessary standards for clinical trials and the production of high-quality cell-based products. This could include helping the private sector ensure that stem cell therapies are safe and effective. At the same time, the MoH should implement a strong framework to monitor side effects and complications related to stem cell therapies, with clear evaluation and enforcement for non-compliance. A robust monitoring system will help ensure patient safety and identify potential risks. Once the regulatory framework is in place, the commercialization of stem cell products can be pursued, with a focus on scaling from research to the pharmaceutical industry.

Additionally, Indonesia could benefit from collaborating with countries that have established regulatory frameworks for cell-based therapies. Japan, for example, has specific regulations for regenerative medicine, where the Pharmaceutical and Medical Devices Agency (PMDA) conducts scientific reviews, and the Ministry of Health, Labor and Welfare (MHLW) approves or withdraws marketing authorizations (Carolina et al., 2022). They also regulate conditional approval to expedite the marketing authorization process. While in Taiwan, although the Regenerative Medicinal Product Act is still in draft, there are several Act from the Taiwan Food and Drug Administration (TFDA) that regulate the medical practice and products to increase accessibility while also implementing compassionate treatment for stem cells (Abolarinwa et al., 2021). By sharing experiences and aligning with international standards, Indonesia can strengthen its regulations and ethical guidelines, ensuring patient safety and facilitating the translation of stem cell, cell, and its derivaties research into clinical use.

Finally, it is essential for trusted media outlets to accurately share information about stem cell, cell, and its derivaties therapies, educating the public on the potential benefits, risks, and ethical considerations involved. This will increase awareness and trust in stem cell, cell, and its derivaties treatments and support the growth in Indonesia.

Conclusion

In Indonesia, the regulation of stem cell therapies and their derivatives is overseen by both the Ministry of Health (MoH) and the Indonesian FDA. The MoH focuses on the clinical application of stem cell, cell-based therapies, ensuring their safe and effective use in medical settings. Meanwhile, the Indonesian FDA regulates the production process and marketing authorization of stem cell products within the country. Several regulatory structures for cell-based therapy highlight the necessity for collaboration between academics, the business sector, doctors/collegiums, the government, and media. This collaborative effort is essential for ensuring patient safety, improving access to therapies, promoting research, raising public awareness, and helping Indonesia achieve self-sufficiency in producing and utilizing cell therapies. This aligns with the government's broader health reforms, which aim to strengthen the country's healthcare system and promote independence in health services

References

- Abolarinwa, B. A., Shaw, M. K., & Lee, C. H. (2021). Perspectives on Challenges to Cell Therapy Development in Taiwan: Strengthening Evidential Standards and Ways Forward. Frontiers in Bioengineering and Biotechnology, 9. https://doi.org/10.3389/fbioe.2021.789043
- Brembilla, N. C., Modarressi, A., André-Lévigne, D., Brioudes, E., Lanza, F., Vuagnat, H., Durual, S., Marger, L., Boehncke, W.-H., Krause, K.-H., & Preynat-Seauve, O. (2022). Efficacy and safety of a patch containing adipose-derived stem cells for skin wound healing-results form a comprehensive pre-clinical evaluation program. bioRxiv.https://doi.org/10.1101/2022.03.09.483580
- Carolina, I. L., Antònia, A., Mercè, O., & Antonio, V. (2022). Regulatory and clinical development to support the approval of advanced therapies medicinal products in Japan. In Expert Opinion on Biological Therapy (Vol. 22, Issue 7, pp. 831–842). Taylor and Francis Ltd. https://doi.org/10.1080/14712598.2022.2093637
- Chen, Y. C., Cheng, H. F., & Yeh, M. K. (2017). Cell therapy regulation in Taiwan. In Cell Transplantation (Vol. 26, Issue 3, pp. 483–492). Cognizant Communication Corporation. https://doi.org/10.3727/096368916X693293
- Chouw, A., Facicilia, G., Arofah, A. N., Kirana, M. N., Dirgantara, Y., Jundan, S. F., Alifah, Z., Sartika, C. R., & Mutia, S. (2021). 413 Regulatory Affairs, Quality Systems, Policy, and Ethics STANDARD REGULATION FOR STEM CELL PRODUCTS IN INDONESIA. In Abstracts / Cytotherapy (Vol. 23).
- George, B. (2011). Regulations and guidelines governing stem cell based products: Clinical considerations. Perspectives in Clinical Research, 2(3), 94. https://doi.org/10.4103/2229-3485.83228
- González-González, A., García-Sánchez, D., Dotta, M., Rodríguez-Rey, J. C., & Pérez-Campo, F. M. (2020). Mesenchymal stem cells secretome: The cornerstone of cell-free regenerative medicine. World journal of stem cells, 12(12), 1529–1552. https://doi.org/10.4252/wjsc.v12.i12.1529
- Han, Y., Yang, J., Fang, J., Zhou, Y., Candi, E., Wang, J., Hua, D., Shao, C., & Shi, Y. (2022). The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. In Signal Transduction and Targeted Therapy (Vol. 7, Issue 1). Springer Nature. https://doi.org/10.1038/s41392-022-00932-0
- Ibrahim, M. F. G., & Allam, F. A. F. A. (2022). Potential stem cell—Conditioned medium and their derived exosomes versus omeprazole in treatment of experimental model of gastric ulcer. Acta Histochemica, 124(4). https://doi.org/10.1016/j.acthis.2022.151896
- Mathur, S., & Hoskins, C. (2017). Drug development: Lessons from nature. Biomedical Reports, 6(6), 612–614. https://doi.org/10.3892/br.2017.909
- Mendes-Pinheiro, B., Anjo, S. I., Manadas, B., Da Silva, J. D., Marote, A., Behie, L. A., Teixeira, F. G., & Salgado, A. J. (2019). Bone Marrow Mesenchymal Stem Cells' Secretome Exerts Neuroprotective Effects in a Parkinson's Disease Rat Model. Frontiers in Bioengineering and Biotechnology, 7. https://doi.org/10.3389/fbioe.2019.00294
- Mousaei Ghasroldasht, M., Seok, J., Park, H. S., Liakath Ali, F. B., & Al-Hendy, A. (2022). Stem Cell Therapy: From Idea to Clinical Practice. In International Journal of Molecular Sciences(Vol. 23, Issue 5). MDPI. https://doi.org/10.3390/ijms23052850
- Vizoso, F. J., Eiro, N., Cid, S., Schneider, J., & Perez-Fernandez, R. (2017). Mesenchymal stem cell secretome: Toward cell-free therapeutic strategies in regenerative medicine. InInternational Journal of Molecular Sciences (Vol. 18, Issue 9). MDPI AG. https://doi.org/10.3390/ijms18091852

Tony Yu-Xiu Lin, Thai-Yen Ling Ph.D.
Graduate Institute of Pharmacology, National Taiwan University College of Medicine, Taiwan

IMAGE FROM CANVA.COM

Global MSC Clinical Trial and Products: A Comprehensive Review as of 2025

As of early 2025, mesenchymal stem cell (MSC) therapies have made remarkable strides in the field of regenerative medicine, offering hope for a wide range of medical conditions. However, this progress has not come without its challenges. From 2010 to now, thirteen MSC products have been approved (Table 1) [1, 2]. The development of MSC-based therapies has been marked by significant breakthroughs, particularly in the approval of key products such as Prochymal (Canada, New Zealand) in 2012 and Cartistem (South Korea) for osteoarthritis. Following these early successes, therapies like Alofisel (EU, Japan, 2018) for complex perianal fistulas in Crohn's disease and Temcell (Japan, 2015) for acute graft-versus-host disease (aGVHD) further expanded the therapeutic applications of MSCs (Table 1). However, Alofisel was later withdrawn from the EU market in 2024 due to concerns over its efficacy and safety, as announced by the European Medicines Agency (EMA) [3]. Despite this setback, the development of MSC therapies continued, though the period after 2018 has seen no new MSC products reaching approval until Ryoncil in 2024, highlighting a period of stagnation in product development.

TABLE 1. GLOBAL OVERVIEW OF APPROVED MSC PRODUCTS AS OF 2025

Drug Name	Year of Approval	Country	Indication	MSC Source	Transplant Type
Queen-cell	2010	South Korea	Connective tissue disorders	Adipose Tissue	Autologous
Cellgram-AMI	2011	South Korea	Acute Myocardial Infarction	Bone Marrow	Autologous
Prochymal	2012	Canada, New Zealand	Acute Graft-Versus-Host Disease (aGVHD)	Bone Marrow	Autologous
Cartistem	2012	South Korea	Knee Cartilage Defects and Osteoarthritis	Umbilical Cord Blood	Allogenic
Cupistem	2012	South Korea	Complex Crohn's Disease with Perianal Fistulas	Adipose Tissue	Allogenic
NeuroNata-R	2014	South Korea	Amyotrophic Lateral Sclerosis (ALS)	Bone Marrow	Autologous
Holoclar	2015	EU	Limbal stem cell deficiency due to ocular burns	Limbus	Autologous
Temcell HS	2015	Japan	Acute Graft-Versus-Host Disease (aGVHD)	Bone Marrow	Allogenic
Stempeucel	2017	India	Critical Limb Ischemia due to Buerger's Disease	Bone Marrow	Allogenic
Alofisel (withdrawal in EU in 2024)	2018	EU, Japan	Complex Perianal Fistulas in Crohn's Disease	Adipose Tissue	Allogenic
Mesoestro-Cell	2018	Iran	Osteoarthritis	Bone Marrow	Autologous
Stemirac	2018	Japan	Spinal Cord Injury	Bone Marrow	Autologous
Ryoncil	2024	United States	Steroid refractory acute graft-versus-host disease	Bone Marrow	Allogenic
Amimestrocel	2025	China	Steroid refractory acute graft-versus-host disease	Umbilical Cord	Allogenic

US's First Approved MSC Product

The approval of Ryoncil in 2024 marks a significant milestone for MSC-based therapies. This product was specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients aged two months and older (Table 1) [4]. This approval was made possible through robust clinical evidence that demonstrated Ryoncil's safety and efficacy. The allogeneic bone marrow-derived MSCs in Ryoncil were shown to modulate immune responses effectively, reducing inflammation and improving survival rates in children with SR-aGVHD [5]. The success of Ryoncil underscores the growing trend of targeting well-defined medical indications with clear endpoints, a strategy that MSC developers are increasingly adopting to overcome regulatory hurdles and ensure clinical success. Following the approval of Ryoncil in the U.S., China also took a significant step forward in the field of MSC-based therapies by granting approval in January 2025 for the use of MSCs in treating GvHD [6]. This marks the first such approval in China, further expanding the global reach and recognition of MSC therapies as viable treatments for immune-related diseases like GvHD.

Despite the approval of Ryoncil, the years between 2018 and 2024 were marked by regulatory and technical bottlenecks that hindered the approval of new MSC-based products. Regulatory agencies worldwide raised concerns about the variability in MSC products derived from different sources, such as bone marrow, adipose tissue, and umbilical cord. Manufacturing inconsistencies and the complex immunological properties of MSCs further complicated the approval process [1, 7, 8]. Additionally, the long-term safety and efficacy of MSC products needed to be better understood before new therapies could be approved. These challenges, combined with difficulties in meeting clinical trial endpoints, slowed the progress of new MSC products during this period.

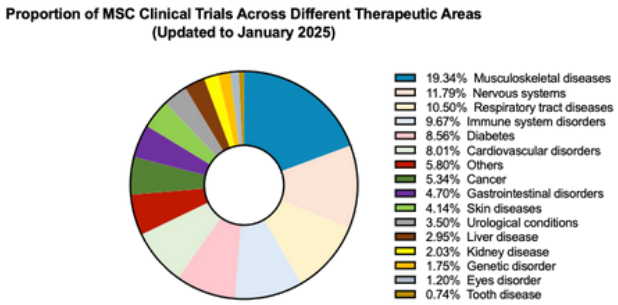


Figure 1. The distribution of MSC clinical trials across various therapeutic areas.

Global Overview of MSC Clinical Trials

The landscape of MSC clinical trials, however, has been much more dynamic. As of early 2025, a total of 1,716 MSC-related trials were identified through data from ClinicalTrials.gov [9], reflecting the substantial global investment in MSC research. These trials encompass a wide array of therapeutic areas, including autoimmune diseases, neurological disorders, oncology, and regenerative treatments for musculoskeletal injuries (Figure 1) [10]. Among the 976 filtered trials, 92 were classified as 'not yet recruiting', 219 were actively recruiting participants, 75 were ongoing but no longer recruiting, and 589 were completed. The large number of completed trials underscores the growing body of evidence supporting MSC therapies, while the 66 terminated trials highlight the inherent challenges involved in conducting MSC clinical research.

Challenges and Prospectives of MSC Clinical Trials

The exponential growth in MSC clinical trials illustrates the expanding scope of MSC research ((Figure 2). Asia, in particular, has emerged as a leader in MSC clinical trials. Countries such as China, Japan, Taiwan, and South Korea, are not only leading in trial registrations but are also at the forefront of MSC product development (Figure 3). This region has seen the successful commercialization of products like Temcell and Alofisel, while several other clinical trials continue to explore the potential of MSCs for treating a variety of complex conditions. However, despite this progress, MSC trials face persistent challenges, including heterogeneity of MSCs, various patient characteristics, heterogeneity of disease, diversity in clinical trial design [8, 11], and navigating complex regulatory environments that vary significantly across regions.

Another significant hurdle for MSC clinical trials is the lack of universally accepted biomarkers to predict therapeutic efficacy. While MSCs are widely regarded for their immunomodulatory and regenerative properties, the mechanisms through which they exert their effects are not yet fully understood [11]. This lack of clarity complicates the design of trials with clear, measurable outcomes, especially for chronic diseases where MSC effects are more gradual and multifactorial. These challenges necessitate the development of more refined trial designs and endpoints, which can accurately measure the therapeutic potential of MSCs in diverse patient populations.

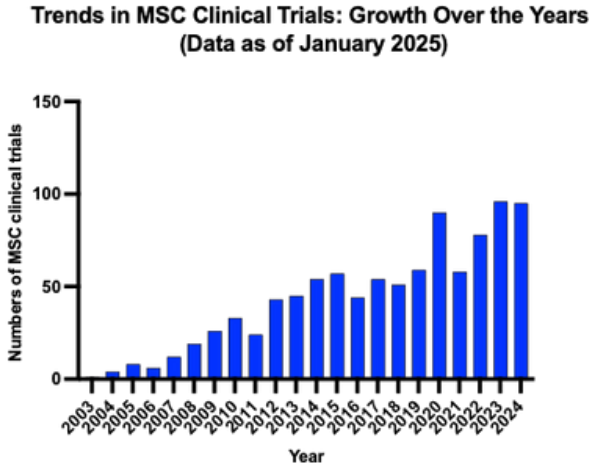


Figure 2. increasing number of MSC clinical trials over the years, with a noticeable upward trend in the more recent years.

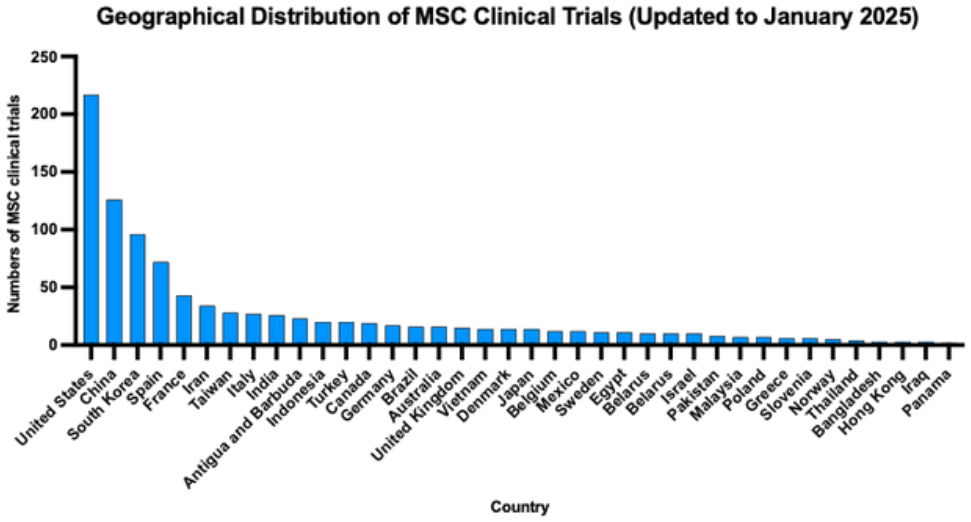


Figure 3. The number of mesenchymal stem cell (MSC) clinical trials conducted across various countries.

In response to these challenges, new trends are emerging in MSC research, including the development of engineered MSCs and extracellular vesicle-based therapies. These innovative approaches seek to enhance the therapeutic efficacy and safety of MSC treatments. By engineering MSCs or utilizing their extracellular vesicles, researchers aim to provide more targeted and effective therapies with fewer risks [1]. Additionally, these approaches address scalability challenges, offering off-the-shelf solutions that do not rely on live cell delivery, making them potentially more accessible for patients.

Future Direction

The application of advanced imaging techniques and artificial intelligence (AI)-based analysis is also providing new insights into the behavior of MSCs and their mechanisms of action [12, 13]. These technologies are enabling researchers to identify key factors that influence treatment outcomes and improve the overall design of clinical trials.

As MSC clinical trials continue to expand and evolve, international collaboration will be crucial in overcoming the remaining hurdles in this field. Harmonizing regulatory standards, sharing clinical data, and addressing the translational gap between research and clinical application will be essential to realizing the full potential of MSC-based therapies. The integration of novel technologies, such as gene editing and bioinformatics, will further optimize MSC therapies for a broader range of medical indications.

With continued global effort and collaboration, MSC-based therapies hold the potential to transform the treatment landscape for some of the most challenging medical conditions, offering new hope for patients worldwide.

References

1. Johnson, J., Shojaee, M., Mitchell Crow, J., & Khanabdali, R. (2021). From mesenchymal stromal cells to engineered extracellular vesicles: a new therapeutic paradigm. Frontiers in Cell and Developmental Biology, 9, 705676.
2. Fernández-Garza, L. E., Barrera-Barrera, S. A., & Barrera-Saldaña, H. A. (2023). Mesenchymal stem cell therapies approved by regulatory agencies around the world. Pharmaceuticals, 16(9), 1334.
3. European Medicines Agency. (2024, January 7). Alofisel withdrawn from the EU market. European Medicines Agency.
4. U.S. Food and Drug Administration (FDA) (February 2024). FDA approves first mesenchymal stromal cell therapy to treat steroid-refractory acute graft-versus-host disease. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-approves-first-mesenchymal-stromal-cell-therapy-treat-steroid-refractory-acute-graft-versus-hostknow.
5. Kurtzberg, J., Abdel-Azim, H., Carpenter, P., Chaudhury, S., Horn, B., Mahadeo, K., ... & MSB-GVHD001/002 Study Group. (2020). A phase 3, single-arm, prospective study of remestemcel-L, ex vivo culture-expanded adult human mesenchymal stromal cells for the treatment of pediatric patients who failed to respond to steroid treatment for acute graft-versus-host disease. Biology of Blood and Marrow Transplantation, 26(5), 845-854.
6. China's NMPA clears country's first mesenchymal stem cell therapy (January 2025). Bioworld.https://www.bioworld.com/articles/716203-chinas-nmpa-clears-countrys-first-mesenchymal-stem-cell-therapy?v=preview.
7. Mei, R., Wan, Z., Yang, C., Shen, X., Wang, R., Zhang, H., ... & Su, H. (2024). Advances and clinical challenges of mesenchymal stem cell therapy. Frontiers in Immunology, 15, 1421854.
8. Mastrolia, I., Foppiani, E. M., Murgia, A., Candini, O., Samarelli, A. V., Grisendi, G., & Dominici, M. (2019). Challenges in clinical development of mesenchymal stromal/stem cells: concise review. Stem cells translational medicine, 8(11), 1135-1148.
9. U.S. National Library of Medicine. (n.d.). ClinicalTrials.gov: Search results for Mesenchymal Stem Cells. Retrieved January 2025, from https://clinicaltrials.gov/searchterm=Mesenchymal%20Stem%20Cells&aggFilters=status:act%20com%20not%20rec.
10. Maldonado, V. V., Patel, N. H., Smith, E. E., Barnes, C. L., Gustafson, M. P., Rao, R. R., & Samsonraj, R. M. (2023). Clinical utility of mesenchymal stem/stromal cells in regenerative medicine and cellular therapy. Journal of biological engineering, 17(1), 44.
11. Li, Y., Hao, J., Hu, Z., Yang, Y. G., Zhou, Q., Sun, L., & Wu, J. (2022). Current status of clinical trials assessing mesenchymal stem cell therapy for graft versus host disease: a systematic review. Stem Cell Research & Therapy, 13(1), 93.
12. Zhou, T., Yuan, Z., Weng, J., Pei, D., Du, X., He, C., & Lai, P. (2021). Challenges and advances in clinical applications of mesenchymal stromal cells. Journal of hematology & oncology, 14, 1-24.
13. Shan, Y., Zhang, M., Tao, E., Wang, J., Wei, N., Lu, Y., ... & Wang, G. (2024). Pharmacokinetic characteristics of mesenchymal stem cells in translational challenges. Signal Transduction and Targeted Therapy, 9(1), 242.

Trang Q. T. Pham, Rita Yen-Hua Huang
International Ph.D. Program in Cell Therapy and Regenerative Medicine, TMU
TMU Research Center for Cell Therapy and Regeneration Medicine,
Department of Biochemistry and Molecular Cell Biology, TMU
College of Medicine, TMU

IMAGE FROM CANVA.COM

Ryoncil (Remestemcel-L) Receives U.S. FDA Approval: A Groundbreaking Advancement in Cell and Gene Therapy

The challenges associated with cell and gene therapy (CGT) products have always been significant and continue to evolve. However, the outlook for patients with debilitating and life-threatening diseases has improved with the emergence of promising novel therapies, including CGT products. Among these, allogeneic hematopoietic stem cells (HPCs) have received U.S. Food and Drug Administration (FDA) approval for use in allogeneic hematopoietic cell transplantation (allo-HSCT), effectively treating various malignant and non-malignant conditions. Approved HPC products include HPC-Cord Blood, Ducord, Allocord, Clevecord, Omisirge UBC, and StemCyte's Regenecyte. Consequently, allo-HSCT has significantly enhanced treatment options for pediatric and young patients with hematologic malignancies (1).

Despite these advancements, acute graft-versus-host disease (aGVHD) remains a major complication of allo-HSCT, leading to considerable morbidity and mortality in pediatric patients (2, 3). Systemic corticosteroids are the standard initial treatment for aGVHD; however, only about 50% of patients respond to this therapy (4, 5). In a cohort of 158 cases, aGVHD occurred in 20% of patients, with severity ranging from grade II to IV (6). Notably, 51% (n = 81) of these patients exhibited steroid-refractory aGVHD (SR-aGVHD), and tragically, 47% of these children experienced fatal outcomes during the study (6).

An analysis of pediatric patients with a mean age of 8 years (range 0.3-18.9) who underwent allo-HSCT between 1989 and 2017 and later developed steroid-refractory IV aGVHD shows limited or no improvement in long-term outcomes following aGVHD treatment (7). These findings suggest that while steroids can be effective for aGVHD, they are inadequate, particularly for grade III-IV cases. There is an urgent need for more effective treatments, especially for recipients with SR-aGVHD.

Mesenchymal stem cell (MSC) therapy has emerged as an immune modulator for treating various disorders. Promising outcomes from basic research and case reports have led to numerous clinical trials evaluating the effectiveness of MSCs for acute graft-versus-host disease (aGVHD). However, the results have been controversial.

Prochymal, which consists of allogeneic bone marrow-derived mesenchymal stem cells (BM-MSCs) from healthy adult donors aged 18 to 30, was acquired by Mesoblast (Australia) from Osiris Therapeutics (Columbia, MD, USA) in 2013. In 2012, it received approval from Health Canada and New Zealand to treat pediatric patients under 18 with aGVHD, based on the results of a phase III trial of allogeneic BM-MSCs for treating steroid-refractory aGVHD (NCT00366145) (8). This made Prochymal the first approved drug containing an active MSC ingredient. Although Prochymal was approved under a strict Notice of Compliance with Conditions (NOC/c), which limits its use, numerous allogeneic cellular products are now being developed globally to target not only graft-versus-host disease but also autoimmune diseases and cancers.

In contrast, JR-031 (TEMCELL® HS), developed by JCR Pharmaceuticals in Japan under a license from Osiris, is widely available and utilized in Japan. This product demonstrated favorable clinical outcomes in phase I/II and II/III trials and received full approval from the Japanese Ministry of Labour and Welfare in September 2015 as the first allogeneic product approved for treating patients of all ages with steroid-refractory acute graft-versus-host disease (SR-aGVHD). It was also added to the national health insurance reimbursement list in November 2015 (9).

Since its approval, Temcell has been administered to 381 patients in a 2021 evaluation study, with a median infusion dose of 2 × 10^6 cells per kilogram (10). Among the 306 assessed patients, 56% achieved an overall response rate (ORR) within 28 days of starting MSC therapy. The ORR was 61% in the 151 aGVHD patients who received Temcell as second-line therapy after steroid treatment. The ORR at 6 months for the 381 patients was 40%. These findings support Temcell as a potential treatment for SR-aGVHD, pending the development of new therapies that offer improved survival outcomes (10).

Intriguingly, Remestemcel-L (Prochymal, now Ryoncil), developed in the United States, has achieved a significant milestone as the first mesenchymal stem cell (MSC) therapy approved by the U.S. FDA for treating steroid-refractory acute graft-versus-host disease (SR-aGVHD). Remestemcel-L was evaluated as an alternative treatment for SR-aGVHD in a multicenter study (NCT00759018) involving 241 pediatric patients, most of whom had not responded to multiple immunosuppressive treatments prior to entering the study (11). The overall response rate (ORR) at day 28 was 65%, with responders showing a significantly higher survival rate at day 100 (82%) compared to non-responders (39%) (11). No safety concerns were identified, and the infusions were well tolerated.

The phase III, open-label, multicenter study, conducted across 20 centers in the United States, aimed to assess the efficacy and safety of Remestemcel-L in pediatric patients with aGVHD who had failed steroid treatment and were not receiving additional immunosuppressive therapies. This clinical trial, which included 54 pediatric patients who underwent allo-HSCT, demonstrated promising results for treating aGVHD in children at high risk of SR-aGVHD using allogeneic BM-MSC therapy (12). Remestemcel-L therapy resulted in a significantly higher day 28 ORR of 70.4%, which remained statistically significant through day 100 compared to the control group. The complete response rate ranged from 29.6% at day 28 to 44.4% by day 100. Remestemcel-L was well tolerated, with no adverse reactions related to infusion or safety issues reported. In summary, Remestemcel-L provides compelling evidence supporting its safety, tolerance, and effectiveness as an initial treatment for pediatric aGVHD following the failure of steroid therapy.

Regarding the approval of Ryoncil (Remestemcel-L) by the U.S. FDA, Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research, stated, "Today's decision marks an important milestone in the use of innovative cell-based therapies to treat life-threatening diseases that have devastating impacts on patients, including children." The FDA's approval of the first MSC therapy not only paves the way for the development of safe and effective cell and gene therapy (CGT) products but also holds significant promise for enhancing the quality of life for patients suffering from debilitating diseases.

References

- Phelan R, Chen M, Bupp C, Bolon YT, Broglie L, Brunner-Grady J, et al. Updated trends in hematopoietic cell transplantation in the united states with an additional focus on adolescent and young adult transplantation activity and outcomes. Transplant Cell Ther. 2022; 28:409.e1-409.e10.
- 2. Zeiser R and Blazar BR. Acute graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med. 2017; 377:2167-2179.
- 3. Mohty M, Holler E, Jagasia M, Jenq R, Malard F, Martin P, et al. Refractory acute graft-versus-host disease: a new working definition beyond corticosteroid refractoriness. Blood. 2020; 136:1903-1906.
- 4. Garnett C, Apperley JF, and Pavlů J. Treatment and management of graft-versus-host disease: improving response and survival. Ther Adv Hematol. 2013; 4:366-378.
- 5. Westin JR, Saliba RM, De Lima M, Alousi A, Hosing C, Qazilbash MH, et al. Steroid-refractory acute gvhd: predictors and outcomes. Adv Hematol. 2011; 2011:601953.
- 6. Verbeek AB, Jansen SA, von Asmuth EGJ, Lankester AC, Bresters D, Bierings M, et al. Clinical features, treatment, and outcome of pediatric steroid refractory acute graft-versus-host disease: a multicenter study. Transplant Cell Ther. 2022; 28:600.e1-600.e9.
- 7. Berger M, Pessolano R, Carraro F, Saglio F, Vassallo E, and Fagioli F. Steroid-refractory acute graft-versus-host disease graded III-IV in pediatric patients. A mono-institutional experience with a long-term follow-up. Pediatr Transplant. 2020; 24:e13806.
- 8. Reicin C, McMahon E, and Chung C. Stem cell therapy regulation in Canada: implications of the prochymal approval. Westlaw J. 2012; 28:1-4.
- 9. Najima Y and Ohashi K. Mesenchymal stem cells: the first approved stem cell drug in Japan. 日本造血細胞移植学会雑誌. 2017; 6:125-132.
- 10. Murata M, Terakura S, Wake A, Miyao K, Ikegame K, Uchida N, et al. Off-the-shelf bone marrow-derived mesenchymal stem cell treatment for acute graft-versus-host disease: real-world evidence. Bone Marrow Transplant. 2021; 56:2355-2366.
- 11. Kurtzberg J, Prockop SE, Prasad VK, Chaudhury S, Teira P, Nemecek ER, et al. Effect of human mesenchymal stem cells (Remestemcel-L) on clinical response and survival confirmed in a large cohort of pediatric patients with severe high-risk steroid-refractory acute graft versus host disease. Biol Blood Marrow Transplant. 2016; 22:S59.
- 12. Kurtzberg J, Abdel-Azim H, Carpenter P, Chaudhury S, Horn B, Mahadeo K, et al. A phase 3, single-arm, prospective study of Remestemcel-L, ex vivo culture-expanded adult human mesenchymal stromal cells for the treatment of pediatric patients who failed to respond to steroid treatment for acute graft-versus-host disease. Biol Blood Marrow Transplant. 2020; 26:845-854.

Vijetha Karen Kitchley
International PhD program in cell therapy and regenerative medicine,
Taipei Medical University

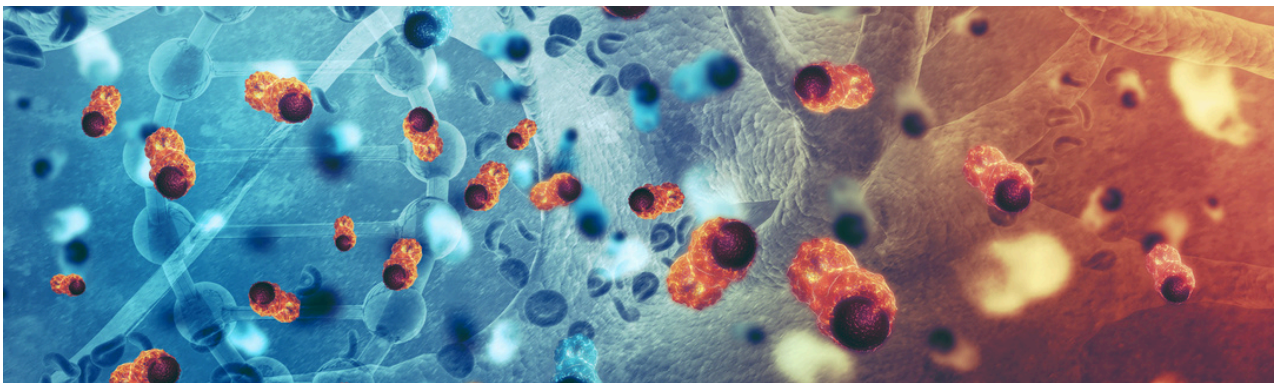


IMAGE FROM CANVA.COM

Exosomes as Next-Generation Drug Delivery Vehicles

Biogenesis, Mechanisms of Cellular Uptake, and Drug Loading Approaches in Therapeutic Applications

Exosomes

Exosomes are small extracellular vesicles, ranging from 30 to 150 nm in size, with a characteristic phospholipid bilayer. They are secreted by both prokaryotic and eukaryotic cells, serving as crucial mediators for intercellular communication and signaling (fig 1)[1]. Initially, exosomes were considered simple cellular waste products. However, further studies have highlighted their significant role in cellular communication, as they carry a variety of proteins, metabolites, and nucleic acids across different cells in the organism [2, 3].

The process of exosome biogenesis is complex and involves multiple stages in the endosomal pathway. It begins with endocytosis, where the plasma membrane invaginates, forming early endosomes that mature into late endosomes. As maturation proceeds, inward budding of the membrane in multivesicular bodies (MVBs) leads to the creation of intraluminal vesicles (ILVs) inside these bodies [1]. During this stage, proteins, lipids, and nucleic acids from the cytoplasm are integrated into the vesicles. These vesicles then fuse with the cell membrane, releasing the ILVs as exosomes into the extracellular space. Alternatively, ILVs may merge with lysosomes for content degradation [2].

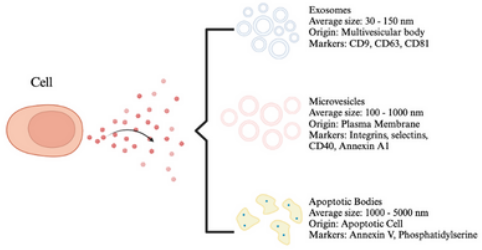


Figure 1 Classification of extracellular vesicles

Cellular Uptake of exosomes

Once exosomes are released into the extracellular space, they interact with target cells, with various factors such as cell types and surface molecules influencing this interaction. While the exact mechanisms of exosome uptake remain unclear [3], it is believed that upon reaching the target cell, exosomes may enter through endocytosis, direct membrane fusion, or receptor-mediated endocytosis, leading to intracellular signaling pathway activation.

Endosomal escape refers to the process by which exosomal cargo is released into the cytosol to exert its effects. If the cargo is endocytosed, it stays within the endosomes, which may either degrade the contents via lysosomal action or secrete them back into the extracellular space without affecting the recipient cell [4, 5]. Direct fusion with the plasma membrane is thus considered a preferable method for drug delivery applications, allowing for the release of exosomal contents, including proteins, lipids, RNA, and drugs, into the cytosol, where they can impact cellular function. This influence may manifest as changes in gene expression, modifications of signaling pathways, or immune response activation.

Exosome uptake can also occur through interactions between specific proteins on the exosome surface and receptors on target cells. Although the precise mechanisms remain under investigation, several surface proteins on exosomes, such as fibronectin, tetraspanins, and immunoglobulins, play vital roles in facilitating targeting [6-8].

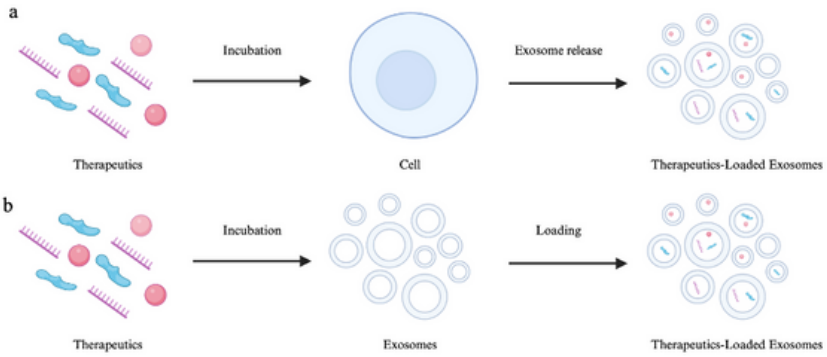


Figure 2 Passive loading of therapeutic materials (a) cell based and (b) non-cell based

Proteins like PD-L1, TNF, and TRAIL, found on tumor cell surfaces, hold promise for cancer therapy. However, variability across different cell types presents challenges for the clinical use of exosome-based drug delivery systems [9]. Nevertheless, ongoing research continues to explore the potential of exosomes as innovative drug delivery vehicles due to their ability to transport therapeutic agents effectively into cells [10].

Drug loading

Exosomes have shown lower toxicity and immunogenicity compared to synthetic nanoparticles in preclinical studies, making them a safer option for drug delivery systems. Their high biocompatibility and stability, attributed to their cellular origin and lipid bilayers, offer protection against degradation by enzymes and harsh physiological conditions, including low pH. Furthermore, exosomes are capable of reaching target organs through the bloodstream and can cross the blood-brain barrier (BBB) to deliver therapeutic agents [11]. Several strategies have been explored to load exosomes with therapeutic materials, optimizing their use as drug delivery platforms. These strategies typically involve either passive or active loading methods [12].

Passive loading

In passive loading, therapeutic agents are introduced into cultured cells, where they are naturally incorporated into the forming exosomes (fig. 2). The cells absorb the drug and encapsulate it within the exosomes, which are then released into the surrounding medium. This method is simple and easy to implement but has lower loading efficiency and less control over the quantity of drug loaded into the exosomes. It is especially effective for lipophilic drugs but may not work well for all types of drugs [12, 13].

Active loading

Active loading involves directly incorporating drugs into isolated exosomes (fig. 3). This approach uses techniques such as sonication, heat shock, electroporation, and detergent incubation to enhance exosome membrane permeability, allowing for higher drug loading efficiency and better control over the drug quantity. However, active loading is a more complex and time-consuming process, and improper handling can damage the exosomes [12, 13].

Regardless of the loading method, purification techniques such as ultracentrifugation, size exclusion chromatography, or ultrafiltration are essential for removing unincorporated drugs. Additionally, genetic engineering can enable the loading of specific genetic materials into exosomes by modifying cells to express particular proteins or RNA sequences, which are then incorporated during exosome formation. This technique allows for precise loading but requires advanced molecular biology techniques and may not be suitable for all therapeutic agents [13]. Each method has its pros and cons, with the optimal choice depending on factors such as drug type, exosome source, and target delivery.

Surface Functionalization Strategies

Natural exosomes, although effective in drug delivery, face challenges such as short half-lives and poor targeting specificity [14]. Surface modification of exosomes can address these issues. Proteins on the exosomal surface can be used as anchors for attaching targeting proteins or peptides through chemical or physical modifications [15]. These strategies, categorized as pre-secretory (e.g., genetic engineering) or post-secretory (e.g., click chemistry and ligand-receptor interactions), enhance the targeting, cellular uptake, and immune evasion properties of exosomes [16].

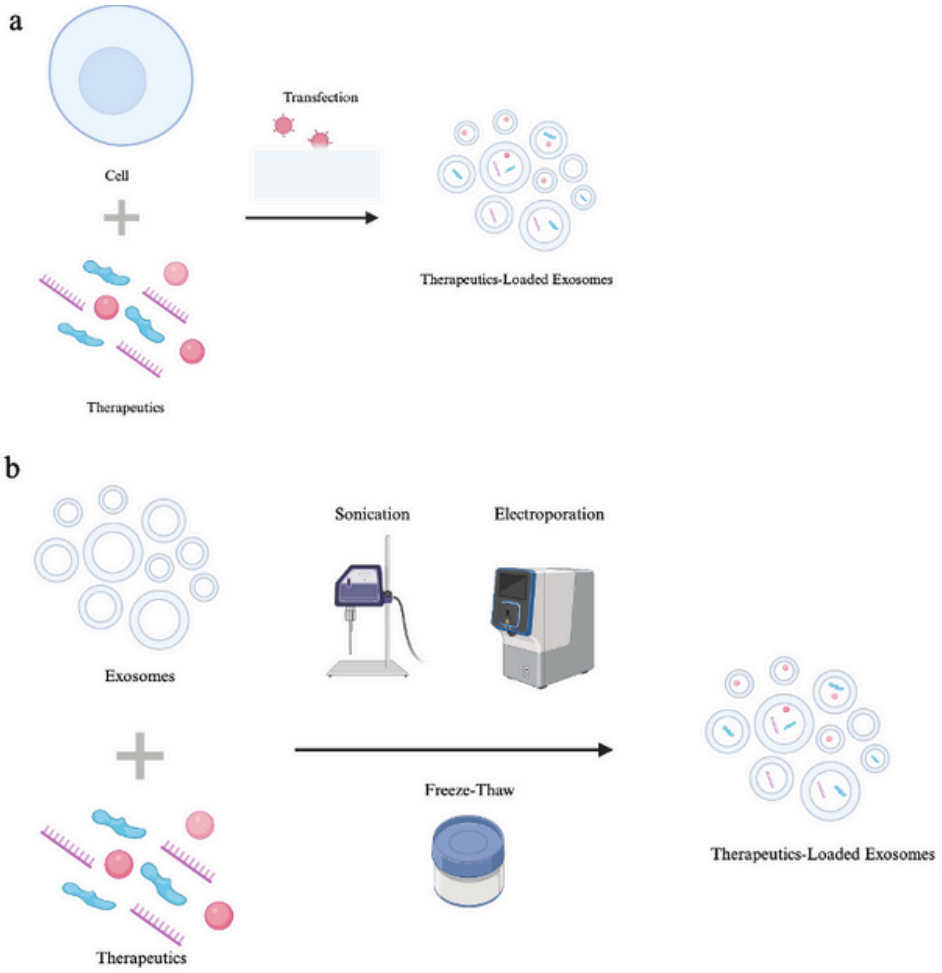


Figure 3 Active loading of therapeutic materials (a) cell based and (b) non-cell based

Genetic Engineering

Genetic engineering involves modifying parent cells to express specific proteins on their exosomal membranes, facilitating targeted drug delivery. This technique, though effective, is time-consuming and may not be suitable for patient-derived exosomes. For example, exosomes derived from HEK293 cells engineered to target Her2-positive tumors have shown promising results in tumor targeting [17]. Similarly, exosomes modified with Lamp1b and iRGD have demonstrated excellent tumor-targeting and therapeutic effects when loaded with DOX [18].

Chemical Modification

Chemical modification uses covalent or noncovalent bonds to attach target proteins to exosome surfaces. Click chemistry is commonly used for covalent bonding and forms stable bonds under physiological conditions, but precise control is required to preserve exosome integrity [19]. For instance, cRGD-Exos targeted ischemic brain lesions and enhanced curcumin delivery in mouse models [20]. Metabolic glycan engineering further supports click chemistry applications [21]. Noncovalent methods, like hydrophobic interactions, offer milder conditions but weaker binding. For example, transferrin-bound exosomes showed enhanced tumor targeting under magnetic fields [22]. Another example, chimeric antigen receptor modified – small extracellular vesicles (sEVs) showed improved therapeutic efficacy for acute liver failure by targeting liver specific marker [23].Such modifications enhance targeting, immune responses, and therapeutic efficiency.

Hybrid Membrane Engineering

This approach fuses functionalized liposomes with exosomes to create hybrid exosomes with enhanced properties [24, 25]. For example, macrophage-derived exosomes combined

with liposomes altered their interaction with cells [26]. Hybrid exosomes can integrate additional features, such as heat sensitivity for tumor-specific drug delivery under hyperthermic conditions [27]. They also facilitate CRISPR/Cas9 delivery to MSCs, overcoming transfection challenges [28].

Conclusion

Despite strong evidence supporting the potential of exosomes as drug delivery systems, natural exosomes exhibit certain limitations, such as heterogeneity, which can reduce therapeutic efficacy and even contribute to tumor progression. To overcome these challenges, engineering modifications are essential. Unlike unmodified exosomes, engineered exosomes with membrane alterations possess specific tumor-targeting capabilities. Moreover, integrating exosomes with other nanomaterials, such as liposomes [29] and polymeric nanocarriers (PNCs),[30] , can enhance therapeutic outcomes through synergistic effects.

Bioinspired or biomimetic exosomes have emerged as promising candidates for clinical applications. However, several challenges must be addressed before their widespread use. First, there is no standardized protocol for isolating, quantifying, and analyzing engineered exosomes from complex biological samples such as blood, tissue, and urine. Second, the precise quantification of exosomes—whether based on exosome count, protein content, their ratio[31], or classical mAb microarray-based surface profiling [32] —remains unresolved. Finally, the selection of the most suitable exosome sources is still unclear, as different exosome types exhibit distinct functions and compositions. Addressing these issues is crucial for the successful clinical translation of exosome-based drug delivery systems.

References

1. Minciacchi, V.R., M.R. Freeman, and D. Di Vizio, Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes. Semin Cell Dev Biol, 2015. 40: p. 41-51.
2. Grant, B.D. and J.G. Donaldson, Pathways and mechanisms of endocytic recycling. Nat Rev Mol Cell Biol, 2009. 10(9): p. 597-608.
3. Xie, S., Q. Zhang, and L. Jiang, Current Knowledge on Exosome Biogenesis, Cargo-Sorting Mechanism and Therapeutic Implications. Membranes, 2022. 12(5): p. 498.
4. Joshi, B.S., et al., Endocytosis of Extracellular Vesicles and Release of Their Cargo from Endosomes. ACS Nano, 2020. 14(4): p. 4444-4455.
5. Polanco, J.C., et al., Exosomes induce endolysosomal permeabilization as a gateway by which exosomal tau seeds escape into the cytosol. Acta Neuropathol, 2021. 141(2): p. 235-256.
6. Purushothaman, A., et al., Fibronectin on the Surface of Myeloma Cell-derived Exosomes Mediates Exosome-Cell Interactions. J Biol Chem, 2016. 291(4): p. 1652-1663.
7. Hazawa, M., et al., Radiation increases the cellular uptake of exosomes through CD29/CD81 complex formation. Biochem Biophys Res Commun, 2014. 446(4): p. 1165-71.
8. Prada, I. and J. Meldolesi, Binding and Fusion of Extracellular Vesicles to the Plasma Membrane of Their Cell Targets. International Journal of Molecular Sciences, 2016. 17(8): p. 1296.
9. Krylova, S.V. and D. Feng, The Machinery of Exosomes: Biogenesis, Release, and Uptake.International Journal of Molecular Sciences, 2023. 24(2): p. 1337.
10. Cecchin, R., et al., Extracellular vesicles: The next generation in gene therapy delivery. Mol Ther, 2023. 31(5): p. 1225-1230.
11. Liang, Y., et al., Cell-derived nanovesicle-mediated drug delivery to the brain: Principles and strategies for vesicle engineering. Mol Ther, 2023. 31(5): p. 1207-1224.
12. Luan, X., et al., Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin, 2017. 38(6): p. 754-763.
13. Han, Y., et al., Overview and Update on Methods for Cargo Loading into Extracellular Vesicles.Processes, 2021. 9(2): p. 356.
14. Smyth, T., et al., Biodistribution and delivery efficiency of unmodified tumor-derived exosomes.Journal of Controlled Release, 2015. 199: p. 145-155.
15. Zhang, Y., et al., Exosome: A Review of Its Classification, Isolation Techniques, Storage, Diagnostic and Targeted Therapy Applications. Int J Nanomedicine, 2020. 15: p. 6917-6934.
16. Kim, H.Y., et al., Functional Extracellular Vesicles for Regenerative Medicine. Small, 2022. 18(36): p. e2106569.
17. Longatti, A., et al., High affinity single-chain variable fragments are specific and versatile targeting motifs for extracellular vesicles. Nanoscale, 2018. 10(29): p. 14230-14244.
18. Wang, C., et al., Engineering a HEK-293T exosome-based delivery platform for efficient tumor-targeting chemotherapy/internal irradiation combination therapy. J Nanobiotechnology, 2022. 20(1): p. 247.
19. Yoon, H.Y., et al., Copper-Free Click Chemistry: Applications in Drug Delivery, Cell Tracking, and Tissue Engineering. Adv Mater, 2022. 34(10): p. e2107192.
20. Tian, T., et al., Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy. Biomaterials, 2018. 150: p. 137-149.
21. Takayama, Y., K. Kusamori, and M. Nishikawa, Click Chemistry as a Tool for Cell Engineering and Drug Delivery. Molecules, 2019. 24(1): p. 172.
22. Qi, H., et al., Blood Exosomes Endowed with Magnetic and Targeting Properties for Cancer Therapy.ACS Nano, 2016. 10(3): p. 3323-33.
23. Lu, Y.-T., et al., Small Extracellular Vesicles Engineered Using Click Chemistry to Express Chimeric Antigen Receptors Show Enhanced Efficacy in Acute Liver Failure. Journal of Extracellular Vesicles, 2025. 14(2): p. e70044.
24. Donoso-Quezada, J., S. Ayala-Mar, and J. González-Valdez, State-of-the-art exosome loading and functionalization techniques for enhanced therapeutics: a review. Crit Rev Biotechnol, 2020. 40(6): p. 804-820.
25. Rayamajhi, S., et al., Macrophage-derived exosome-mimetic hybrid vesicles for tumor targeted drug delivery. Acta Biomater, 2019. 94: p. 482-494.
26. Sato, Y.T., et al., Engineering hybrid exosomes by membrane fusion with liposomes. Sci Rep, 2016. 6: p. 21933.
27. Lv, Q., et al., Thermosensitive Exosome-Liposome Hybrid Nanoparticle-Mediated Chemoimmunotherapy for Improved Treatment of Metastatic Peritoneal Cancer. Adv Sci (Weinh), 2020. 7(18): p. 2000515.
28. Lin, Y., et al., Exosome-Liposome Hybrid Nanoparticles Deliver CRISPR/Cas9 System in MSCs. Adv Sci (Weinh), 2018. 5(4): p. 1700611.
29. Du, Y., et al., Engineered Microglia Potentiate the Action of Drugs against Glioma Through Extracellular Vesicles and Tunneling Nanotubes. Adv Healthc Mater, 2021. 10(9): p. e2002200.
30. Bose, R.J., et al., Engineered Cell-Derived Vesicles Displaying Targeting Peptide and Functionalized with Nanocarriers for Therapeutic microRNA Delivery to Triple-Negative Breast Cancer in Mice.Advanced Healthcare Materials, 2022. 11(5): p. 2101387.
31. Webber, J. and A. Clayton, How pure are your vesicles? Journal of Extracellular Vesicles, 2013. 2(1): p. 19861.
32. Zhang, X., et al., Engineered Extracellular Vesicles for Cancer Therapy. Adv Mater, 2021. 33(14): p. e2005709.

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.

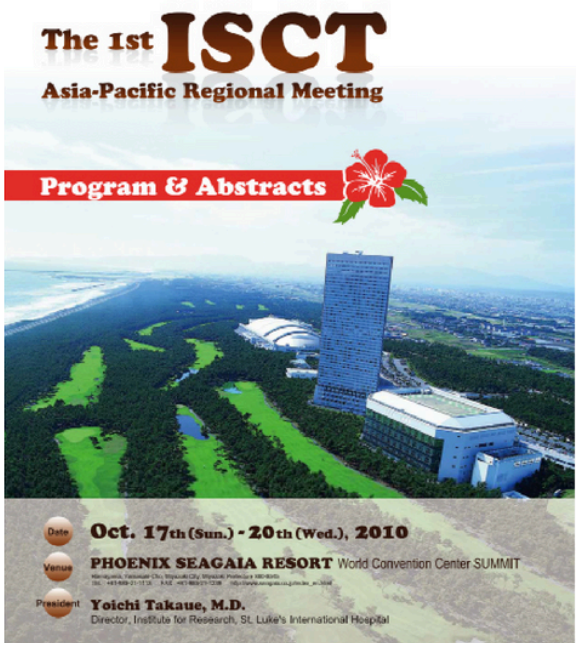
By doing so, ACTO envisions creating a comprehensive ecosystem that accelerates the translation of CGT research into practical applications, benefiting patients and contributing to the broader field of regenerative medicine. Through its activities, publications, and events, ACTO aims to play a crucial 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.

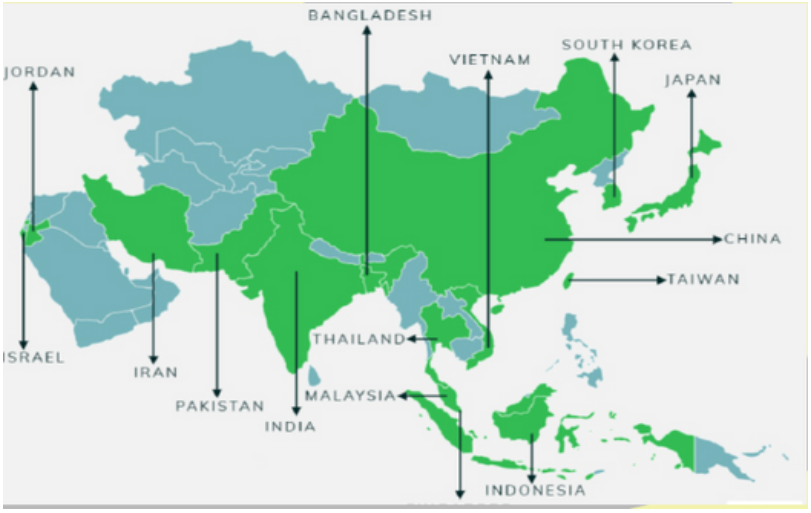
Looking ahead, the ACTO organization remains committed to its regional focus, striving to further expand its presence and influence to better serve the diverse needs of the Asian CGT community.



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.

.

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

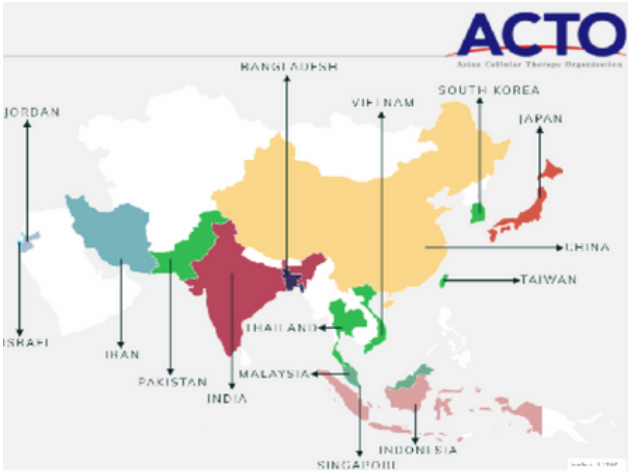
Over the years, the ACTO meetings became a cornerstone for professionals in the field, providing a platform for networking, sharing knowledge, and forging international partnerships. As the organization evolved, reflecting the dynamic landscape of CGT in the Asia-Pacific region.

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.

The ACTO Times
Asian Cellular Therapy Organization

CALL FOR ARTICLES

Spotlight

- **Spring: Singapore**
- **Summer: Vietnam**
- **Fall: South Korea**
- **Winter (New Year Edition): Iran**

Regional CGT regulation, Clinical and Industry, Engineering CGT

Deadline for Submission

- **Spring: 30 March 2025**
- **Summer: 15 June 2025**
- **Fall: 15 September 2025**
- **Winter (New Year Edition): 15 December 2025**

The ACTO Times
Asian Cellular Therapy Organization

CALL FOR

DONATION

CONTACT US

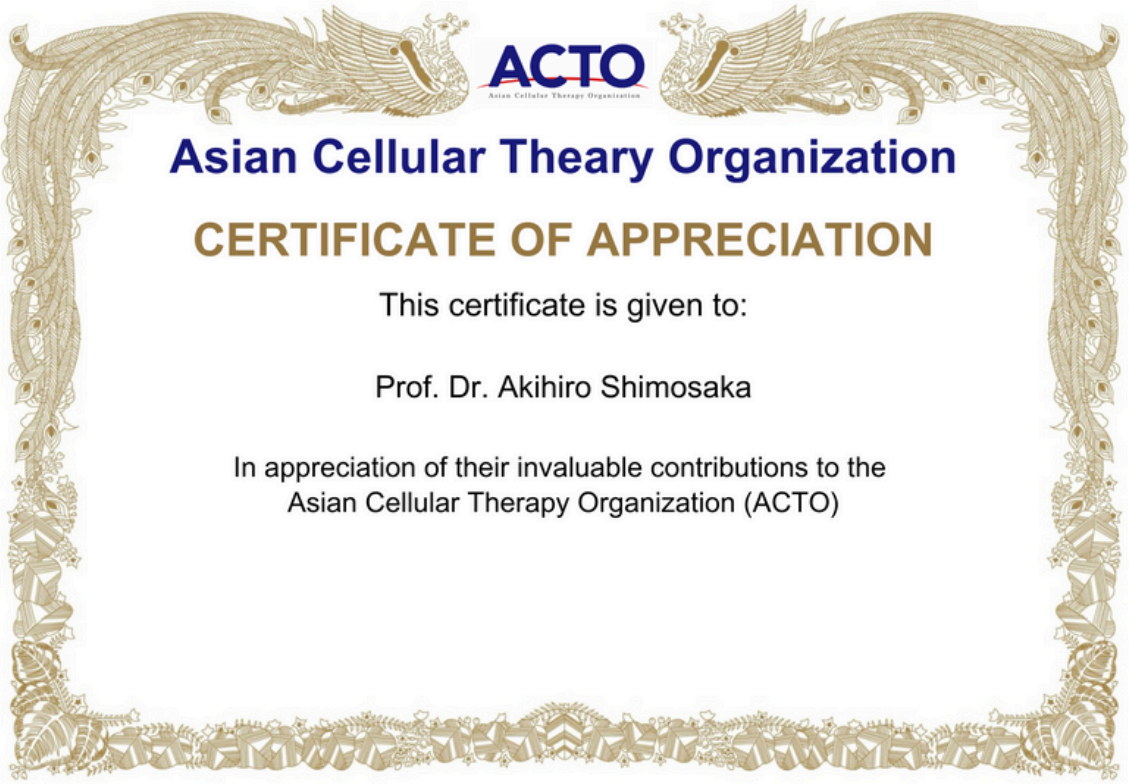
PROF. RITA YEN-HUA HUANG

EDITOR-IN-CHIEF

THE ACTO TIMES

E-mail: <editor@acto-hq.org> |

<at.chiefeditor@gmail.com>



The Certificate of Appreciation for the committee members will be distributed after the approval from the ACTO headquarters.

The ACTO Times

Asian Cellular Therapy Organization

2025 NEW YEAR EDITION