The ACTO Times

Asian Cellular Therapy Organization

VOL. 02
ISSUE 04

The 16th ACTO Annual Congress Report & Highlight

Academic Highlights
Cell Sheet Engineering in Cartilages

CGT Advances & Industrial View
iPSCs clinical trial update, FUTEX Award, Taiwan exosome market, Gwo Xi's Stem Cells

2025 AUTUMN EDITION

The ACTO Times
Asian Cellular Therapy Organization
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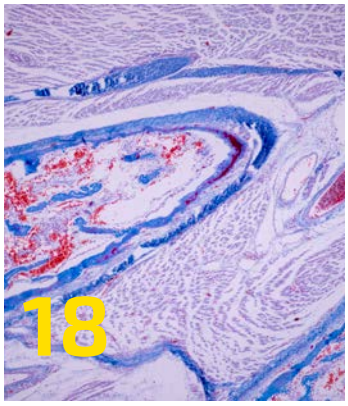

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Greetings
The ACTO Chairperson

Dear ACTO members,

Now we are publishing 2025 ACTO Times Autumn edition. I almost start writing the preface for this edition, just received the news, I am very sad to share this news with you regarding Prof. Yao Chan Chen who passed away on Nov. 17, 2025 in Taipei. He was the pioneer in cell therapy as well as hematology who achieved the first allogeneic stem cell transplantation in Taiwan. Recently he is known as novelist writing the novels based on Taiwan history, specially focusing Taiwan original races.

He is the one of four scientists who joined the cell therapy meeting held in Mulhouse, France 1992. He joined this meeting as a member, then later, this meeting became ISCT. So, he was the original members of the ISCT. I met him in Mulhouse first time and since that day, we worked together. He had been a leader in cell therapy and created TACT for the development of the cell therapy in Taiwan. He also tried to involve regulatory agency for the cell therapy development which made success of the new regulation for cell and gene therapy. This regulation became world second regulation for cell and gene therapy in the world.

For ACTO, first, we worked for ISCT Asia and started ISCT Asia regional meeting in 2010. However, ISCT HQ wanted to control everything and financially control everything following ISCT HQ standard. But at that time, Asian country members were not able to manage higher registration fee. After long discussion with opinion leaders of ISCT, ACTO started in 2011 in collaboration with ISCT and other similar society. Prof. Chen had been a key member of the ACTO establishment for the development of cell therapy in Asia via ACTO activity. We lost key valuable member in the field of cell therapy.
Wishing his eternal peace and condolence to his family.

Sincerely

Chairperson, Asian Cellular Therapy Organization (ACTO)
Akihiro Shimosaka, Ph.D.

Editor's Column

The ACTO Times Editor-in Chief

Dear ACTO Members and Readers of The ACTO Times,

Time flies, and it is now December 2025. This year, we have made significant advances in Asian cell and gene therapy (Asian CGT), highlighted by the great success of the 2025 ACTO Singapore Annual Meeting. However, it is with deep sadness that we share the news of the passing of Vice President Prof. Yao Chan Chen, a key figure in ACTO and The ACTO Times, in November. We extend our heartfelt condolences to his family and hope that Prof. YC Chen rests in peace.

The 2025 Singapore ACTO Annual Meeting brought together regulatory representatives from the EU and various Asian countries to engage in comprehensive reports and discussions on the regulations, clinical practices, and industry aspects of global CGT. A particular focus was placed on regulatory dialogues concerning CGT products and processes, which are driving the rapid alignment of regulations across different countries.

Globally, regulations are aligning, recognizing CGT as "pharmaceuticals." As of the first half of 2025, there are about 120 CGT products worldwide, with the U.S. having the most at 45, followed by the EU and countries like Japan and South Korea with over 20 each, China with 12, India with 7, and Taiwan and Singapore with 6 each.

Taiwan's dual-track regenerative medicine law balances patient rights and CGT precision medicine, complemented by health insurance policies, earning international praise. Japan leads in iPSC clinical translation and allogeneic cell sheets, with conditional product approvals expected. Singapore has strong R&D capabilities, while Indonesia, with its large population, is focusing on stem cell clinical trials under HALAL regulations. India, a major pharmaceutical producer, has 7 approved CGT products, showcasing significant potential. Thailand has approved its first gene therapy product, Zolgensma, and is considering CAR-T Kymriah.

China has made significant progress in the CAR-T field. Although it approved its first CD19 CAR-T product Axi-cell in 2021, four years after the U.S., by 2025, China has approved 10 domestically developed CAR-T products, priced at $140,000-$180,000, about one-third of the U.S. product Kymriah. The next generation of CAR-T products is expected to be priced around $40,000, making CGT more accessible. Additionally, China's NMPA has approved the first gene therapy product for hemophilia B and an allogeneic umbilical cord mesenchymal stem cell product for SR-GvHD.

Gene therapy is proving effective in rare disease treatment. In 2020, Jimi Olaghere successfully underwent CRISPR gene editing for sickle cell disease, leading to FDA approval of Casgevy and Lyfgenia in 2023 for sickle cell disease and β-thalassemia. In May 2025, CRISPR technology achieved another breakthrough by treating an infant with CPS1 deficiency, a rare metabolic disorder; Zolgensma, approved by the FDA in 2019 for spinal muscular atrophy (SMA), has shown remarkable efficacy. By early 2025, over 3,700 patients have received Zolgensma treatment, with significant results. In September, the FDA introduced the Rare Disease Evidence Principles (RDEP) to expedite drug approval for rare diseases affecting fewer than 1,000 patients, using single-arm clinical trial data.

Editor's Column
The ACTO Times Editor-in Chief

The global CGT market funding reached $5.1 billion in the first quarter of 2025. North America leads with $4.4 billion, followed by the EU with $800 million, and the Asia-Pacific region with the lowest at $500 million, accounting for one-tenth of the total funding. Despite this, Asia is demonstrating strong resilience and ambition in the CGT field. Out of 2,070 CGT companies worldwide, Asia has 750, closely following North America's 770. The number of clinical trials in Asia has reached 840, tying with North America for the global lead.

The rise of CGT in Asia is poised to remove barriers for underserved patients, offering new hope and opportunities.

Sincerely,

Yen Hua Huang, PhD
Distinguished Professor, Taipei Medical University
Editor-in-Chief, The ACTO Times
ACTO, Asian Cellular Therapy Organization

IN LOVING MEMORY OF

Prof. Yao Chan Chen

17.11.2025

In Memoriam: Professor Yao Chan Chen (1949–2025)

It is with heavy hearts that we announce the passing of a true hero in the fields of hematology and cell therapy, Professor Yao-Chan Chen. A pioneer, a visionary leader, and a cherished colleague, Prof. Chen left an indelible mark on the medical landscape of Taiwan and the world.

Prof. Chen was not only the pioneer who achieved the first allogeneic stem cell transplantation in Taiwan, but he was also a bridge-builder who connected Asian science to the global community. From his early days as one of the original founding members of the International Society for Cell & Gene Therapy (ISCT) to his pivotal role in establishing the Asian Cellular Therapy Organization (ACTO), his life was dedicated to advancing patient care and scientific collaboration.

Beyond his medical legacy, Prof. Chen was a celebrated novelist whose passion for Taiwan's history and indigenous cultures inspired a generation to rediscover their roots.
To those of us who had the privilege of working alongside him—some since that first historic meeting in Mulhouse in 1992—he was a mentor, a partner, and a dear friend. We have lost a key, valuable member of our community, but his legacy will live on in the regulations he shaped, the organizations he built, and the lives he saved.

We extend our deepest condolences to his family and wish him eternal peace.

The ACTO Times
on behalf of Asian Cellular & Therapy Organization (ACTO)

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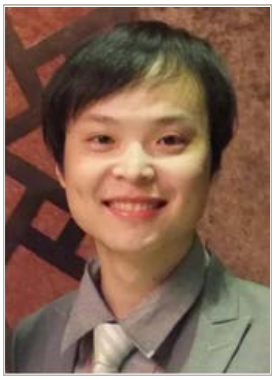

Yung-Che Kuo, PhD
Taipei

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.

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Reno is a PhD Student in International PhD Program in Medicine, Taipei Medical University. His research focuses on molecular medicine especially related to tumor niche / microenvironment and their role in cancer therapy.

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

Tony Yu-Xiu Lin, MS
Taipei

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

UNVEILING THE TIMELESS TAPESTRY

THE CHRONICLE OF ACTO THROUGH TIME

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

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

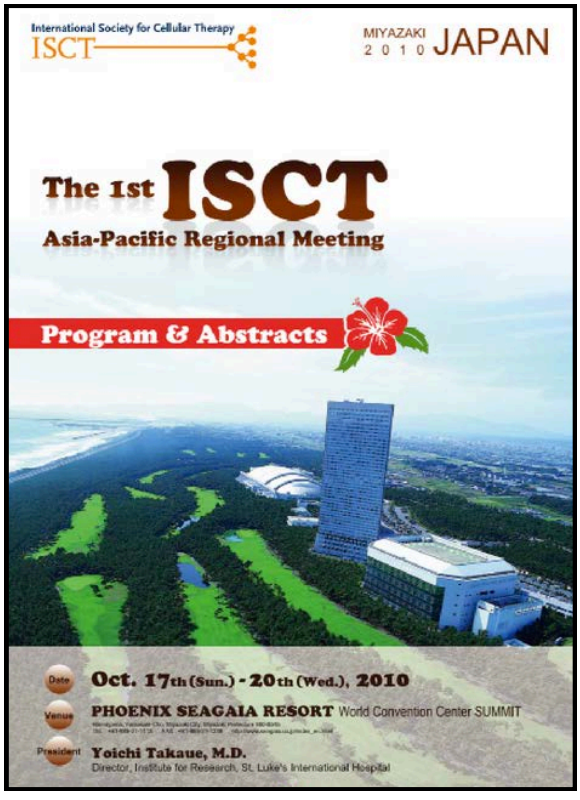
By doing so, ACTO envisions creating a comprehensive ecosystem that accelerates the translation of CGT research into practical applications, benefiting patients and contributing to the broader field of regenerative medicine. Through its activities, publications, and events, ACTO aims to play a crucial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

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

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

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

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



PRELUDE

NAVIGATING THE UNIQUE DYNAMICS OF CGT IN ASIA

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

Large Population Dynamics

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

Gene Background Diversity

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

Culture-Related Pre-Clinical Research

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

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Manufacturing and Industry Evolution

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

Regulatory Frontiers

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

OUR JOURNEY THROUGH TIME

IMAGE FROM CANVA.COM

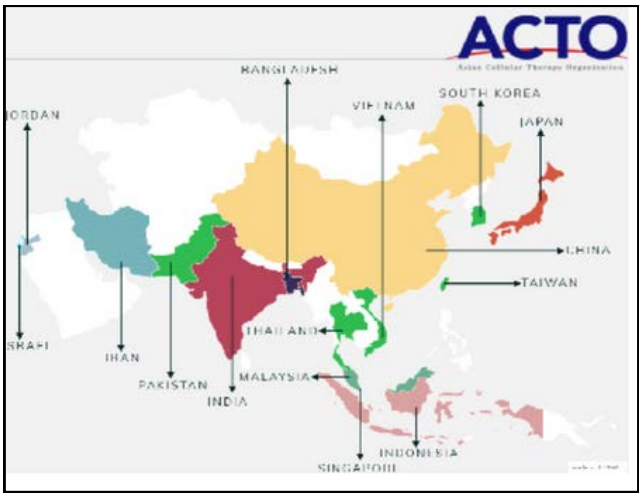
Over the years, the ACTO meetings became a cornerstone for professionals in the field, providing a platform for networking, sharing knowledge, and forging international partnerships. As the organization evolved, reflecting the dynamic landscape of CGT in the Asia-Pacific region.

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

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

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

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



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

2025 16th ACTO Annual Meeting Report

Yunxin Chen[1], Francesca LWI Lim[1], Srinivasan Kellathur[2] & Mickey B.C. Koh[3]

[1]Singapore General Hospital and National Cancer Centre, Singapore
[2]Roche Singapore Technical Operations, Singapore
[3]City St Georges, University of London, UK and St George's University Hospital, London, UK

From Left to Right: Adj Asst Prof Srinivasan Kellathur (Local Organizing Committee Member), Dr Stefaan Van der Spiegel (Plenary Speaker), Prof Mickey Koh (ACTO President), Dr Cheong Wei Yang (Guest-of-Honor), Professor Christian Chabannon (Plenary Speaker), Prof Akihiro Shimosaka (ACTO Chairperson), Clin Asst Prof Francesca Lim (Local Organizing Committee Member), Clin Asst Prof Chen Yunxin (Local Organizing Committee Member)

The 16th Annual Meeting of the Asian Cellular Therapy Organization (ACTO) was held in Singapore from 14–16 August 2025, and brought together leading scientists, clinicians, regulators, and industry partners across the Asia-Pacific region. The meeting focused on the latest advances in cell and gene therapy, regional manufacturing capabilities, and provided a platform to discuss and address real-world challenges of affordability.

This year's meeting showcased the region's growing strength in scientific innovation and translational capability and sought collaborative efforts to accelerate cell therapy in Asia. The conference opened with a welcome address by Guest of Honour Dr Cheong Wei Yang, Chairman of the Board Oversight Committee of the Advanced Cell Therapy and Research Institute, Singapore (ACTRIS) — Singapore's key facility for GMP-grade cell manufacturing. Dr Cheong highlighted Singapore's commitment to drive innovation through regional and international partnerships, emphasizing how these are vital to building a sustainable ecosystem for advanced therapeutics.

Global Perspectives and Regional Lessons

The plenary session featured two distinguished international speakers who provided invaluable global perspectives. Professor Christian Chabannon shared insights from the GoCART Coalition, a pan-European initiative that unites stakeholders across academia, industry, and regulatory agencies to maximize the potential of cellular immunotherapies. Such structured collaboration and harmonized practices may serve as a reference for Asia's rapidly evolving cell therapy landscape. Dr Stefaan Van der Spiegel, from the European Commission, followed with a discussion on the EU framework for Substances of Human Origin (SoHO) — offering important lessons on the regulatory integration of cell and gene therapies, and considerations for policy development in Asia.

Scientific and Translational Advances

The scientific program covered a broad and dynamic range of topics, including CAR-T cells and other immune effector cell therapies such as mesenchymal stromal cells, exosomes, and gene therapy. There were also industry-led sessions highlighting advances in manufacturing technologies, process optimization, and novel therapeutic platforms. Sessions on regenerative medicine showcased emerging applications in cartilage repair, skin regeneration, and ocular therapies amongst others, reflecting the expanding indications of cell-based interventions beyond oncology.

A regional highlight of the meeting was the country update session, where representatives from various Asian nations presented progress reports on clinical programs and regulatory pathways. The presentations reflected both diversity and growth — illustrating how different countries are advancing toward shared goals of accessible, safe and efficacious cell therapy.

Regulatory and Translational Focus

Among the most anticipated sessions was the Regulatory Panel Session: "Pursuing Cell Therapy Approval in the Region", which generated enthusiastic audience participation. The discussion, detailed in a companion article, explored pathways and strategies for navigating evolving regulatory frameworks across Asia. The session reinforced the importance of ongoing dialogue between innovators and regulators to translate promising therapies safely and efficiently into clinical practice.
Ethics of cell and gene therapy was also explored together with equity of access to such novel yet costly therapies.

Delegates also gained insight into translating cell therapy products from bench to bedside. A guided visit to ACTRIS provided participants with a closer look at Singapore's national cell manufacturing capabilities and its role in supporting both academic and commercial development.

Building Networks and Future Directions

The meeting concluded with strong positive feedback from participants and opened doors for collaboration with ACTO serving as a vital platform for regional exchange, enabling the collective advancement of cellular therapies in Asia. The 16th ACTO Annual Meeting reaffirmed the organization's mission to bridge science, regulation, and clinical practice, fostering a community dedicated to making advanced cell and gene therapies accessible to patients across the region. We look forward to the next meeting ACTO 2026 set to take place in Jakarta, Indonesia.

Photo Courtesy of ACTO 2025 Organizers

2025 16th ACTO Annual Meeting Highlights

Eddie HP Tan [1], James Leong [1], Srinivasan Kellathur [2]

[1] Centre of Regulatory Excellence, Duke-NUS Medical School, National University of Singapore, Singapore
[2] Roche Singapore Technical Operations, Singapore

From Left to Right: Asst Prof Eddie Tan (Duke-NUS Centre of Regulatory Excellence), Dr Maria Cristina Galli (Formerly ISS, Italy), Dr Yoshiaki Maruyama (PMDA Japan), Ms Christine Ho (HSA Singapore), Mrs Tri Asti Isnariani (Indonesian FDA), Mr Morakot Papassiripan (Bureau of Drug Control of Food and Drug Administration, Thailand), Ms Chia-Ping Liu (Taiwan FDA), Adj Asst Prof Srinivasan Kellathur (Roche Singapore)

Bringing Regulations into Focus at ACTO 2025

ACTO 2025 in Singapore delivered 2 high-powered sessions on Day 2 of the conference, focusing on regulatory matters. In Regulatory Session 1 chaired by Dr Yoshiaki Maruyama (PMDA, Japan), Prof Dr Taruna Ikar (Food and Drug Authority, Indonesia) opened with a keynote lecture on the newly established Regulatory Framework of Advanced Therapy Medicinal Products (ATMP) in Indonesia. Valuable insights and regional regulatory updates were shared by regulators and regulatory experts from Japan, Thailand, Singapore, Taiwan, Italy and Malaysia. The presentations for Japan and Taiwan highlighted dual-track approaches, risk-based regulation with conditional approval pathways and robust research support consortia, and showed the continued commitment to facilitate access to ATMP innovations. The regulators from Thailand, Singapore, and Malaysia showcased their respective frameworks integrating international standards, GMP certification, and early-stage developer consultations, emphasizing harmonization and patient safety. The European approach mandates centralized authorization for ATMPs across the European Commission member countries, continuous pharmacovigilance, and employs tools like PRIME and hospital exemptions for early access.

Chaired by Adj Asst Prof Srinivasan Kellathur and Asst Prof Eddie Tan, the Regulatory Session 2 brought back the regulatory experts, namely Mrs Tri Asti Isnariani (Indonesian FDA), Dr Yoshiaki Maruyama (PMDA, Japan), Mr Morakot Papassiripan (Bureau of Drug Control of Food and Drug Administration, Thailand), Ms Christine Ho (HSA, Singapore), Ms Chia-Ping Liu (Taiwan FDA, Taiwan), Dr Maria Cristina Galli (formerly Istituto Superiore di Sanita, Italy) for a panel discussion. The exchanges examined regulatory approaches across Asia and Europe in advancing frameworks for regenerative medicine and advanced therapy medicinal products (ATMPs). Japan's conditional approval system demonstrates innovation but requires further adaptation, while Thailand and Indonesia are building internationally aligned structures emphasizing early consultation and expanded GMP certification. Singapore employs a flexible, risk-based model supporting both clinical and hospital-based applications. Discussions on patient access highlighted the growing role of hospital exemptions in Europe, offering controlled yet affordable pathways. Experts emphasized that sustained regulator–developer dialogue, regional harmonization, and proactive industry engagement are essential to ensure safe, efficient, and innovative ATMP development.

The ACTO 2025 Annual Meeting at Singapore

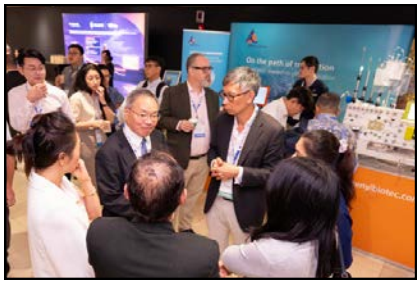


Photo Courtesy of ACTO 2025 Organizers

Junko Matsuo & Setsuko Hashimoto
CellSeed Inc., Tokyo, Japan

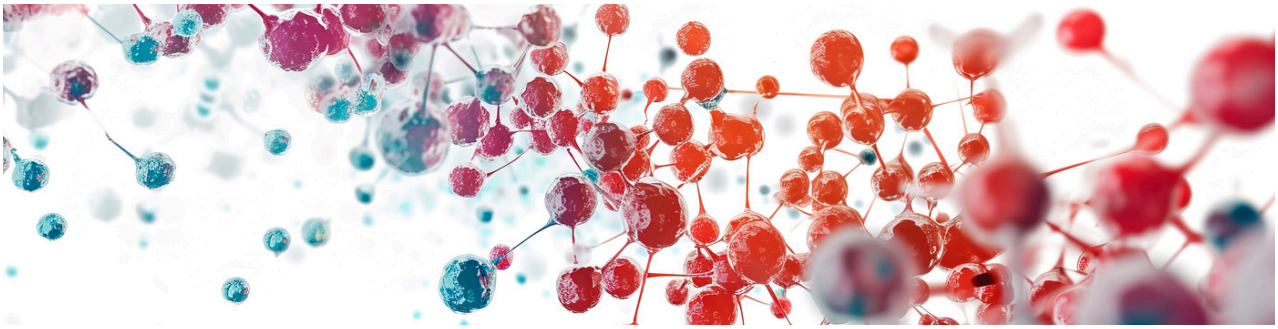


IMAGE FROM CANVA.COM

Cell Sheet Engineering for Cartilage Regeneration in Japan

Abstract
Cell sheet engineering has emerged as a powerful approach for cell therapy including cartilage regeneration. We summarize the feature of cell sheet using temperature-responsive cell cultureware, and its clinical application and highlight the regulatory frameworks of regenerative medicine in Japan. We also introduce our allogeneic chondrocyte sheet (CLS2901C), which is currently undergoing a Phase III clinical trial. We describe our experience overcoming practical challenges in developing the allogeneic chondrocyte sheet for approval under the Act on Pharmaceuticals and Medical Devices (PMD Act) in Japan.

Keywords:
Cell Sheet Engineering, Cartilage Regeneration, Allogeneic Chondrocyte Sheet, Japan Regulatory Framework

Regulatory Framework for Regenerative Medicines in Japan

Japan has two laws that govern the implementation of regenerative medicine (Figure 1). For development of marketing authorization purpose, a clinical trial is conducted under the Act on Pharmaceuticals and Medical Devices (PMD Act). As of August 2025, 23 regenerative medical products have been approved. Considering the specific features of cell therapy products, an early approval system (Conditional and Time-Limited Approval) has been established under the PMD Act. Six products have been approved using the system, yet no products have received full approval. For the technologies whose efficacy and safety have not yet been established, Act on the Safety of Regenerative Medicine (Safety Act) can be applied. For example, clinical research mainly conducted by academia, is regulated by the Safety Act. Advanced Medical Care B (corresponding to the law to the Regulation Governing the Application of Specific Medical Examination Technique and Medical Device in Taiwan) is also regulated by the Safety Act. Private insurance offers an option to cover the cost of Advanced Medical Care B. The Safety Act allowed outsourcing of cell manufacturing, thus enabling CDMO business in Japan.

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Junko is the Head of Cell Sheet CMC Development at CellSeed Inc.
She has about 15 years of experience in cardiac electrophysiological safety testing, utilizing gene-expressing cells, primary myocytes, and iPS cell-derived myocytes. Before joining CellSeed. Inc., she contributed to business development of pre-clinical services in Taiwan.

Setsuko Hashimoto, Ph.D.
Representative Board Director, President/CEO, CellSeed Inc.

Setsuko is President and CEO of CellSeed Inc. She has over 30-year commercial experience in the bio-industry before joining CellSeed. Dr. Hashimoto is well networked globally to academia, government and industry.

Cell Sheet Engineering

Achieving regenerative medicine requires interdisciplinary research across many fields, especially engineering, to prepare cells as cell therapy products. In general, harvesting the adherent cells intact is difficult. Traditionally, cells are harvested using proteolytic enzymes or physical methods such as scraping, which could damage the cells. To solve this problem, Professor Teruo Okano of Tokyo Women's Medical University pioneered the world-first "cell sheet engineering" by introducing temperature-responsive polymer on the surface of the cell cultureware with Nano-Bio Interface technology [1].
This breakthrough innovation was strongly supported by Japanese funding agencies. After cells reach confluence at 37°C, the cells can be detached as intact sheet without damage simply by reducing the temperature to 20°C. These sheet retain cell-cell junctions, adhesive proteins, the extracellular matrix, imparting adhesive characteristics to biological tissues [2].

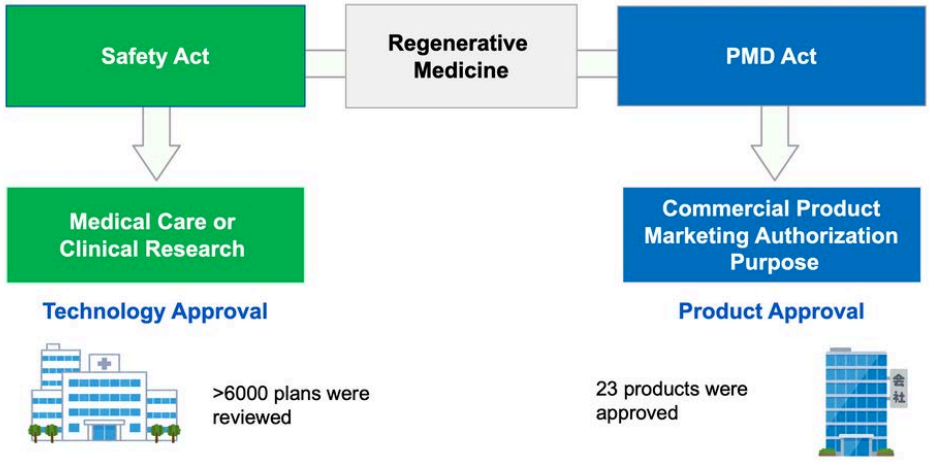

Figure 1. Regulatory framework for Regenerative Medicine in Japan

These are critical to maintain cellular functions and promoting tissue regeneration, and suitable for applications in cell therapy. CellSeed Inc. was established to commercialize "cell sheet engineering". CellSeed is currently engaged in development of regenerative medicine, marketing of temperature-responsive cultureware and the CDMO business. "Cell sheet engineering" is progressing in various clinical applications to cover unmet medical needs (Figure 2), and among 23 approved regenerative medicine products in Japan, three products applied cell sheet engineering.

Cell Sheet Therapy for Cartilage Regeneration

Osteoarthritis, caused by obesity, aging, genetics, occupation, sports, or trauma, is increasing in an aging society. There are an estimated 25 million potential patients in Japan, with 8 million symptomatic cases. Although it is an important disease that should be addressed when considering long-term care costs and medical expenditure, fundamental therapy has not yet been established. Dr. Masato Sato of Tokai University applied cell sheet engineering for cartilage regeneration using chondrocyte sheets. Clinical research revealed the efficacy and safety of autologous chondrocyte sheet. Transplantation of autologous chondrocyte cell sheets along with open-wedge high tibial osteotomy (OWHTO) promoted hyaline cartilage repair [3].

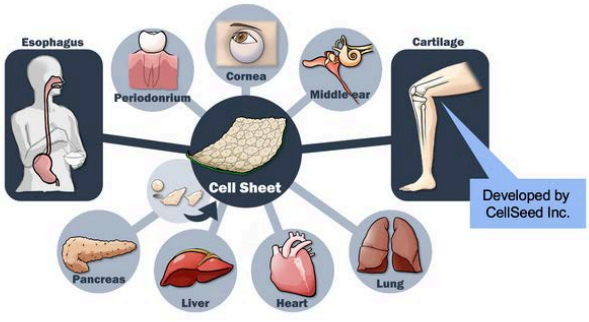

Figure 2. "Cell Sheet Engineering" for Regenerative Medicine

Another clinical research showed that the transplantation of polydactyly-derived allogeneic chondrocyte sheets along with OWHTO improved clinical symptoms with no serious adverse events. The histological examination confirmed regeneration of hyaline cartilage [4]. Allogeneic chondrocyte sheet can eliminate the need for invasive tissue collection, remove restrictions on the knee's damaged area, and ensure a stable cell sheet supply, making treatment available to more patients.

Product Development by CellSeed Inc.

After technology transfer from Tokai University, CellSeed is developing an allogeneic chondrocyte sheet (CLS2901C) to obtain approval under PMD Act in Japan. Since allogeneic cells use excised tissue from patients with polydactyly (extra fingers or toes) as raw materials (Figure 3), it is necessary to address ethical issues. In December 2020, the Ethics Committee of the National Center for Child Health and Development (NCCHD) approved the collection of cartilage tissue from patients with polydactyly for commercial use. This process took approximately two years.

Furthermore, in August 2022, NCCHD and CellSeed reached an agreement for the constant supply and commercial use of excised tissue from polydactyly surgeries. With this agreement, it became possible to obtain the human tissue required for clinical trials and marketing of allogeneic chondrocyte sheet. We established a master cell bank (MCB) of chondrocytes by confirming safety and efficacy. After several consultation with PMDA, we submitted a notification of Phase III clinical trial in Japan in September 2023. For donor selection for MCB, we evaluate the efficacy on cartilage regeneration using the nude rat osteochondral defect model. Although this model is useful in that it enables direct efficacy assessment, it is time-consuming, expensive and has animal welfare issues.

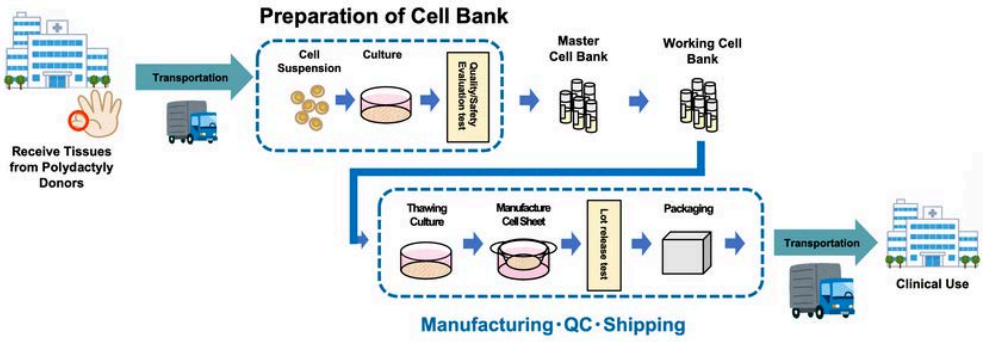

Figure 3. Manufacturing process of Allogenic Chondrocyte Sheet (CLS2901C)

Therefore, we analyzed potential in vitro markers to predict efficacy on cartilage regeneration. We evaluated the correlation between in vivo tissue repair potency scored by histological grading system and the omics data derived from the cell sheet. We extracted several molecules that were highly correlated with in vivo efficacy. In the future, we may replace animal testing and improve quality testing with these markers.

Challenges to Practical Implementation

When companies procure raw materials from medical institutions, various extra, uncompensated tasks arise for the medical institutions. On the company side, the search for and negotiation with cooperating medical institutions is also necessary, which further delays product development. Regenerative medicine products are a new modality with the potential to transform existing treatment concepts. Unlike conventional pharmaceuticals, there are many differences with these products, such as product diversity, unique manufacturing processes and quality control, and an extremely short shelf life. As current regulations may not fully accommodate this new modality, it is crucial to review and update rules to adapt regenerative medicine products.

The Forum for Innovative Regenerative Medicine (FIRM) was incorporated in 2011 to establish social systems that ensure safe and stable access to the benefits of regenerative medicine (https://firm.or.jp/en/). FIRM consists of approximately 200 companies involved in regenerative medicine. FIRM lobbies for improvement of treatment access in consideration of the unique characteristics of regenerative medicine products. For example, approved autologous cell products derived from the patient exhibit variability in raw material quality, which can lead to the production of out-of-specification (OOS) products. OOS products are sometimes administered under compassionate grounds, within the framework of clinical trials in Japan. Although this approach is ethical, it imposes significant operational and administrative burdens on medical institutions and marketing authorization holders, raising concerns about sustainability [5]. The revision to the PMD Act in 2025 introduced an exceptional provision.

Under this measure, the sales and supply of OOS products using autologous cells are permitted solely when certain criteria are fulfilled: product safety is assured, patient needs are considered, and physicians recognize the product's value.

Conclusion

This article introduces the regulatory framework for regenerative medicines in Japan and cell sheet engineering, as well as its applications in cell therapy, including cartilage regeneration. Regenerative medicine products are a new modality with the potential to transform existing treatment concepts. Our allogeneic chondrocyte sheet is also a promising cell therapy product with the potential to treat osteoarthritis at its root.

Many stakeholders are making dedicated efforts towards practical implementation for regenerative medicine. There are many challenges to be addressed, but we hope to resolve these issues through collaboration among industry, regulatory authorities, and academia. Our goal is to deliver better healthcare to the patients.

Acknowledgements

We sincerely thank Dr. Masato Sato (Tokai University), Dr. Akihiro Umezawa, and Dr. Kazuaki Nakamura (National Center for Child Health and Development) for their valuable advice and support.

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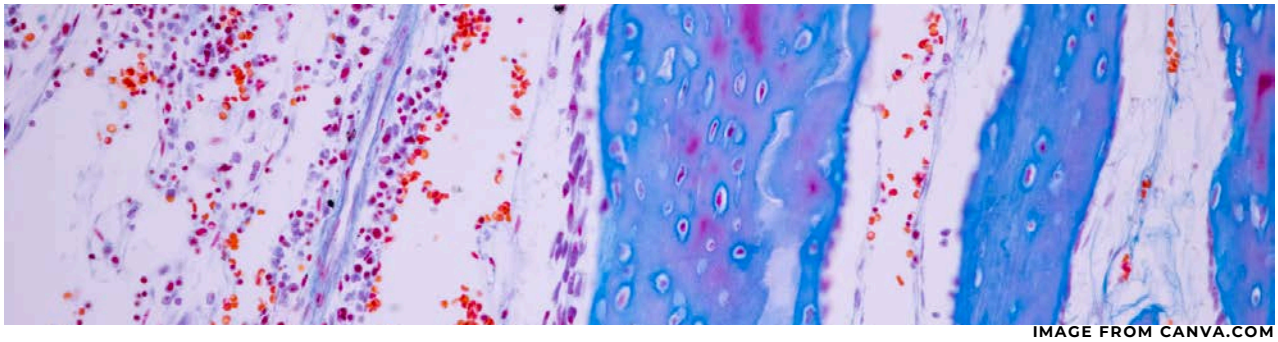

IMAGE FROM CANVA.COM

Cartilage Cell–Sheet Transplantation for Osteoarthritis of the Knee: Toward a Disease-Modifying, Joint-Preserving Therapy

Abstract

Cartilage cell-sheet engineering on temperature-responsive culture surfaces preserves the extracellular matrix (ECM) and enables the sheet to adhere directly and uniformly to chondral defects without a scaffold. As a joint-preserving, disease-modifying approach for osteoarthritis of the knee (OAK), we have advanced both autologous and allogeneic cartilage cell-sheet transplantation from preclinical studies to clinical investigations. Here, we outline methods, outcomes, and the mechanistic basis that support clinical translation.

Background

OAK is a slowly progressive degenerative disease for which disease-modifying, joint-preserving therapies are needed. Cartilage cell sheets fabricated on temperature-responsive culture dishes retain ECM and attach to defects as a 'sheet,' allowing firm coverage of the lesion. In preclinical models, chondrocyte sheets outperformed synovial cell sheets in a rabbit osteochondral defect model; in immunodeficient rats, human chondrocyte sheets induced hyaline-like cartilage regeneration, improved International Cartilage Repair Society (ICRS) histological scores versus controls, and ameliorated pain-related behavior. Efficacy was also confirmed in a large-animal (mini-pig) model.

Methods

Clinically, we first initiated autologous cartilage cell-sheet transplantation in 2013. Building on that experience, we began in 2017 a single-arm, open-label prospective study using allogeneic sheets prepared from polydactyly surgical discards—administered without immunosuppression. The latter combined open-wedge high tibial osteotomy (OWHTO) with bone marrow stimulation (microfracture or abrasion technique) and allogeneic sheet transplantation (the RMSC approach) in 10 patients with Outerbridge grade III–IV OAK. Endpoints included patient-reported outcomes (KOOS and Lysholm Knee Score), MRI-based repair assessment (MOCART 2.0), viscoelastic properties measured by laser-induced photoacoustics (LIPA), and arthroscopic biopsy. The autologous program was accepted in Japan as Advanced Medical Care B in 2019 for further clinical use.

Results

Autologous sheets were transplanted in 20 cases under the Advanced Medical Care B framework, with analyses underway. In the allogeneic cohort, correction of lower-limb alignment was accompanied by improvement in MOCART 2.0 scores. LIPA measurements showed viscoelasticity of the repair tissue approaching that of native cartilage within the same joint. The mean thickness of regenerated cartilage was 3.54 mm. Arthroscopic biopsies at hardware removal showed strong Safranin O staining and COL2 positivity. No serious adverse events were observed. Cells derived from polydactyly tissue exhibited robust proliferation and laminar sheet formation, with surface markers and anabolic factor production comparable to autologous cells, supporting a stable supply chain for an allogeneic regenerative medicine product. An industry-sponsored clinical trial of the allogeneic sheet has been initiated.

Masato Sato, MD, PhD, is Professor and Director with the Department of Orthopaedic Surgery, School of Medicine, Tokai University; the Center for Musculoskeletal Innovative Research and Advancement (C-MIRA), Tokai University Graduate School; and the Tokai University Institute of Medical Sciences. His research focuses on musculoskeletal regenerative medicine and cartilage repair using cell-sheet engineering.

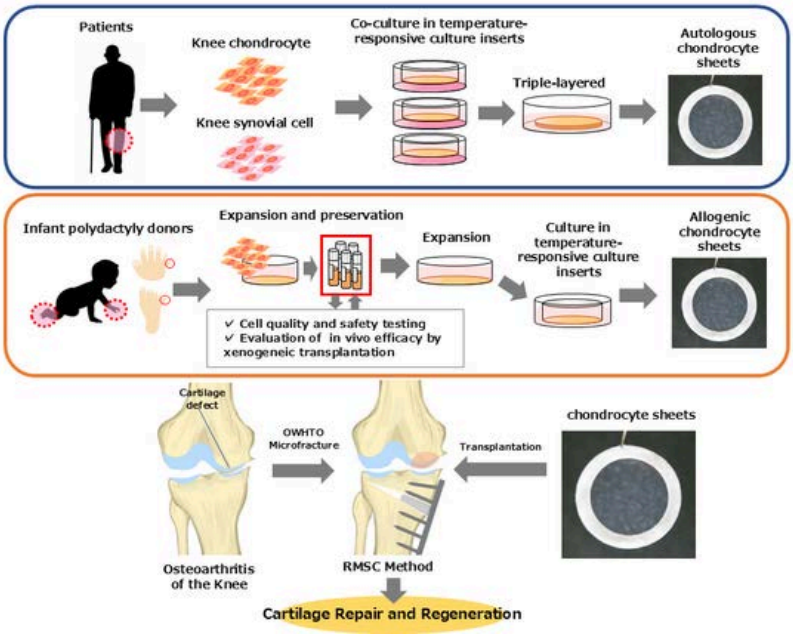

Figure 1. Concept and clinical workflow for autologous and allogeneic cartilage cell sheets. The schematic summarizes sheet fabrication, transplantation alongside OWHTO and marrow stimulation, and multimodal assessments (KOOS/Lysholm, MOCART 2.0 MRI, LIPA viscoelasticity, and arthroscopic biopsy).

Mechanism of Action

Omics-level analyses identified gene sets correlated with clinical outcomes. TGFB1 correlated with KOOS/Lysholm, whereas ESM1 and ACKR4 correlated with histologic scores (OARSI/ICRS II). These factors relate to ECM organization and angiogenic regulation and may serve as biomarkers for donor selection and quality standardization. Preclinically, secreted factors from the sheets—including TGFβ1 and MIA—likely contribute to the pro-regenerative niche.

Conclusions

Cartilage cell-sheet transplantation combines planar adhesion and ECM preservation with paracrine activity. When coupled with alignment correction procedures such as OWHTO, it can improve both symptoms (KOOS/Lysholm) and structure (MOCART 2.0, OARSI/ICRS II), making it a promising disease-modifying, joint-preserving therapy for OAK. While current clinical datasets derive from small, single-arm studies, implementation of biomarker-guided donor selection and quality control is paving the way for practical deployment as an allogeneic regenerative medicine product.

Keywords:
Osteoarthritis of the knee, cartilage cell sheet, allogeneic transplantation, autologous transplantation, open-wedge high tibial osteotomy (OWHTO), MOCART 2.0, laser-induced photoacoustics (LIPA)

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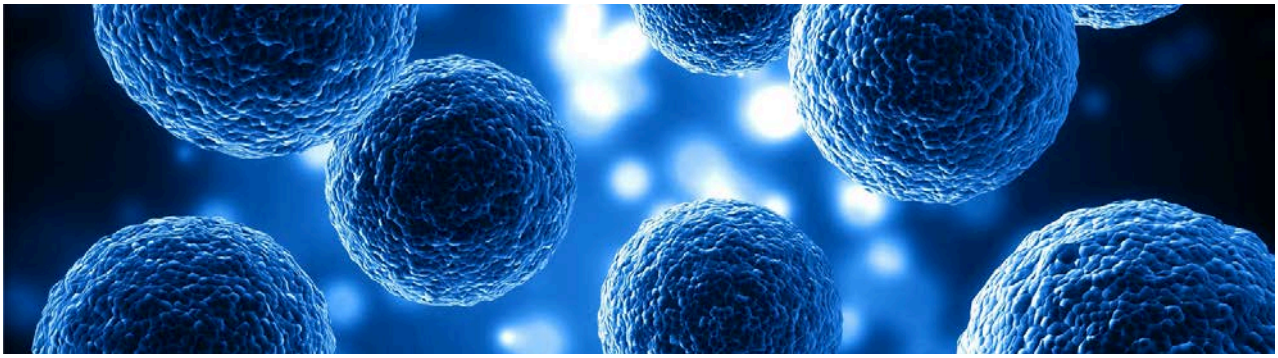

IMAGE FROM CANVA.COM

The post-clinical trial development status of iPSC-derived platelets: Towards the application of the one-and-only universal product

Preface

This year marks the 200th anniversary of the first successful blood transfusions by Dr. James Blundell, saving the lives of four women with severe postpartum bleeding. Today, regenerative medicine using iPSC-derived cells is entering clinical application. In 2020, we completed the iPLAT1 study (jRCTa050190117), the world's first clinical trial of iPSC-derived platelet product (iPSC-PLTs). Building on the success of that study, in which we manufactured "autologous" iPSC-PLTs from the subject's own iPS cells, we are now developing a universal product for the next clinical trial. Specifically, we are working towards HLA-knockout (KO) iPSC-PLTs with improved circulation capacity and more efficient manufacturing procedures to prepare allogeneic formulations. Currently, our group is the only one in the world to have achieved the clinical application of ex vivo-manufactured platelet products. Here, we will outline the current status of our work toward a future clinical trial using universal HLA-KO iPSC-PLTs.

Manufacturing Autologous iPSC-PLTs for the iPLAT Study

Megakaryocytes differentiated from hematopoietic stem cells undergo endomitosis (nuclear division) during maturation, becoming polyploid with approximately 64N chromosomes and reaching a size of 50–100 μm. The expanded cytoplasm forms DMS (demarcation membrane system), leading to platelet production through a fragmentation mechanism or platelet release from the tip of proplatelets—cytoplasmic protrusions extending into bone marrow sinusoids. The number of platelets produced per megakaryocyte is calculated to be between 800 and several thousand.

Professor Koji Eto

Dr. Naoshi Sugimoto

While this platelet production has traditionally been considered to occur primarily in the bone marrow, multiple recent studies have observed a high proportion of platelet production in the spleen and lungs. The in vitro production of platelets essentially equated to solving two key challenges: how to generate a sufficient number of megakaryocytes (present at only about 0.01% in bone marrow) and how to establish a maturation environment that promotes the release of high-quality platelets. We achieved the generation of large quantities of megakaryocytes by leveraging imMKCLs—expandable megakaryocyte progenitor cell lines. imMKCLs are established by introducing expression vectors for the c-MYC, BCL-XL, and BMI1 genes during megakaryocyte differentiation from hematopoietic progenitor cells derived from iPS cells (1).

Expression of these three transgenes is under the control of the Tet-ON system, which induces their expression in response to doxycycline added to the culture media, leading to the robust proliferation of imMKCLs by conferring proliferative, anti-apoptotic, and anti-senescence properties (Dox-ON). Upon depletion of doxycycline, imMKCLs spontaneously mature and release platelets (Dox-OFF).

Furthermore, the development of novel drugs enabling platelet production under liquid culture conditions distinct from the in vivo environment, along with the development of a "turbulent flow" bioreactor, facilitates clinical-scale iPSC-PLT manufacturing (2).

In the iPLAT1 trial, the imMKCL used was established from iPS cells derived from the subject's peripheral blood mononuclear cells. An imMKCL clone with excellent proliferation and platelet production capacity was cryopreserved as the master cell bank (MCB) (3, 4). For iPSC-PLT production, 2×10^6 MCB-imMKCL cells were first cultured in 3 mL medium under the Dox-ON condition. After 23 days, they were amplified to approximately 3×10^{10} cells in a 20 L culture. The medium contained doxycycline, SCF (stem cell factor), and the proprietary thrombopoietin receptor agonist TA-316. Cells were then washed and transferred to Dox-OFF culture using four 8 L VerMES bioreactors (3, 4). This platelet-producing medium contained a ROCK inhibitor and an AhR antagonist to promote maturation and an ADAM17 inhibitor to prevent GPIbα cleavage. Based on in vivo observations, we previously found that turbulent flow is a crucial physical factor contributing to platelet generation from megakaryocytes. To recapitulate similar fluid dynamics, we developed a new culture device, VerMES, with vertical motion, capable of generating turbulence with optimal shear stress and turbulent energy (2).

Six days after Dox-OFF culture, iPSC-PLTs were packaged via megakaryocyte separation and washing/replacement/concentration using a hollow fiber membrane filter and a continuous centrifugation device. The final product contained approximately 1×10^{10} iPSC-PLTs in 200 mL of bicarbonate Ringer's solution/20% ACD/2.5% human serum albumin. Subsequently, to eliminate the tumorigenicity of residual imMKCL, irradiation with 25 Gy of radiation, as is typically done with conventional platelet preparations, was performed (3, 4).

The MCB passed viral safety testing and identity verification, manufacturing additives were confirmed safe based on residual concentration and toxicity/mutagenicity tests, and the final product, iPSC-PLTs, cleared general toxicity testing. In tumorigenicity studies with imMKCLs and iPSC-PLTs, no proliferative cells were detected after 25 Gy irradiation (4). Although iPSC-PLTs were approximately 1.5 times larger than donated platelets (3.5–4 μm), electron microscopy revealed equivalent intracellular structures, and in vitro testing demonstrated comparable quality and function.

Tests in a rabbit model demonstrated competent circulation and hemostatic ability. Distribution tests using fluorescently labeled iPSC-PLTs conducted after completion of the iPLAT1 trial also confirmed systemic circulation (3, 4).

Furthermore, the selection of manufacturing raw materials and development of manufacturing methods in accordance with GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice), as well as the establishment of quality and safety test items, were determined following consultations with the regulatory authority, PMDA (4).

Achievement of Primary Endpoints and Lessons Learned from the iPLAT1 Trial

The iPLAT1 trial, designed as a dose-escalation Phase 1 trial, was approved by Kyoto University and the Ministry of Health, Labour and Welfare, and ultimately, designated as compliant with the Act on the Safety Assurance of Regenerative Medical Treatment in October 2018. It was subsequently registered to the Japan Registry of Clinical Trials as jRCTa050190117 (3).

The study subject was a multiparous woman with aplastic anemia complicated by alloimmune platelet transfusion refractoriness due to anti-HPA-1a antibodies (3). Individuals with the same HPA-1b/1b phenotype compatible for transfusion to this subject constituted less than 0.002% of the Japanese population and were absent among registered donors of the Japanese Red Cross Society. Fortunately, the aplastic anemia itself improved with cyclosporine monotherapy, making it ideal from a safety perspective. Eventually, the iPLAT1 trial was conducted in a stable disease state in which cyclosporine treatment was terminated.

The initial dose of 0.5 Japan units (platelet count 0.1×10^{11}; 1/20th the volume of a standard platelet transfusion) was transfused in May 2019, followed by 1.5 units in August, and 5 units in January of the following year. The primary endpoint was safety, based on the occurrence of adverse events. The secondary endpoint was efficacy, measured by the CCI (corrected platelet increment) values at 1 hour and 24 hours post-transfusion (3). An external safety and efficacy review committee confirmed that there were no issues with dose escalation after the first and second doses. After a one-year observation period following the final dose, the primary endpoint of safety was finally determined to have been successfully achieved. However, the secondary endpoint of CCI did not show a clear post-transfusion increase either at 1 hour or 24 hours (3).

So why did the circulation of iPSC-PLTs not show up in the measurements? At the maximum dose of 5 units, an increase in peripheral blood platelet count should have been measurable. In this regard, we arrived at multiple possibilities. First, reflecting the good control of the underlying disease, the platelet count was already high before transfusion (90,000/μL), making it difficult to detect small changes (3).

Nevertheless, flow cytometry analysis detected the presence of large platelets in blood samples one hour post-transfusion, and their fraction gradually decreased, suggesting that large iPSC-PLTs were circulating (3). In other words, conventional hematology analyzers may have failed to capture the larger iPSC-PLTs.

Alternatively, the peak circulation of iPSC-PLTs might have occurred 2-6 hours post-transfusion—later than conventional platelet transfusions—and the measurement points may not have captured the characteristic temporal changes (3, 4), if circulation dynamics mirrored those observed in animal studies. Collectively, these findings suggest that while iPSC-PLTs were indeed circulating, they were simply not being accurately measured.

We also questioned whether there could be an issue with the circulatory function of the iPSC-PLTs. For example, since the platelets administered in the iPLAT1 trial were autologous preparations, the likelihood of immune rejection was considered extremely low. However, the possibility of antigen modification due to the influence of additives cannot be ruled out.

Following iPSC-PLT transfusion, a slight increase in D-dimer was observed (3), and thus, the possibility that iPSC-PLTs formed thrombi cannot be ruled out. However, no clinical findings suggestive of thrombosis or embolism were noted, nor were thrombi detected by non-invasive lower extremity venous ultrasound. Furthermore, D-dimer levels subsequently decreased spontaneously. However, consistent with the D-dimer course, a transient increase in white blood cell count was also observed (3).

This observation drew attention due to its potential association with thromboinflammation and the contribution of immune megakaryocytes, both identified in severe COVID-19. Recent single-cell RNA sequencing analyses have reported that megakaryocytes in vivo include subsets supporting bone marrow niche maintenance and immune or inflammatory responses. Similarly, since we identified the presence of an immune subset within imMKCLs (5), the possibility that this subset may have induced thromboinflammation warrants further investigation.

Post-iPLAT1 Trial Research and Development

Following the iPLAT1 trial, we set out to perform reverse translational research aimed at fully elucidating the potential deficit in the circulatory function. This effort includes analyzing the presence or absence of anti-iPSC-PLT antibodies and the immune megakaryocyte-like property of imMKCL MCB, as well as verifying low-level platelet activation and desialylation during the manufacturing process.

To advance iPSC-PLTs into a commercially viable formulation, manufacturing processes must also be refined. Currently, imMKCL yields approximately 100 iPSC-PLTs per megakaryocyte cell, which is considered a benchmark for success. However, this falls short of the estimated thousands of platelets produced per megakaryocyte in the body. In this regard, we are considering the suppression or exclusion of immune megakaryocyte-like cells as well as focusing on the allocation of healthy mitochondria to iPSC-PLTs as key factors for improvement. Meanwhile, given that manufacturing based on GCTP allows for the maximum prevention of pathogenic microorganism contamination, there is potential to significantly exceed the current 6-day shelf life of donated platelets if quality can be maintained.

In terms of universal application, we are currently developing HLA class I-deficient iPSC-PLTs toward clinical trials. HLA class I possesses an enormous repertoire, and its incompatibility accounts for the majority of cases of alloimmune platelet transfusion refractoriness, which complicates approximately 5-15% of platelet transfusion patients. HLA-deleted products not only enable safe use in patients with alloimmune platelet transfusion refractoriness but also inherently become a single product, facilitating cost reduction through mass production. They are also well-suited as a foundational platform for specific products like HPA-modified products, functionally engineered products, and platelet-rich plasma (PRP) therapy products. Furthermore, they could serve as an ideal cell base for antibody detection tests during platelet transfusion refractoriness.

In summary, we are developing universal iPSC-PLTs using a manufacturing method that incorporates research and development focused on improving quality by enhancing circulatory capacity and manufacturing efficiency. Our goal is to create a formulation that is truly implementable at the required scales to revolutionize blood transfusion therapy for all patients in the world for the first time in two centuries.

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IMAGE FROM CANVA.COM

From Vision to Innovation: The Spirit of the Taiwan Future Technology Awards

Each year, the Taiwan-based "Future Technology Awards" showcase and honour pioneering technologies with the potential to transform industries, societies and lives. According to the official information for the 2025 edition, the event is part of the Future Tech Pavilion 2025 held at the Taiwan Innotech Expo, a platform for presenting breakthroughs from lab to market [1].

What kind of technologies win? The criteria emphasize innovation, value creation, and integration with Taiwan's industrial strengths — in other words, solutions that are not only scientifically novel but also societally impactful and scalable within Taiwan's ecosystem.

For aspiring entrants or observers of the 2025 awards, the key message is clear: technology must go beyond novelty; it must resonate with application, impact, and strategic relevance. And that is exactly the starting point when we look at advanced biomedical platforms such as extracellular vesicle (EV)-based therapies.

Technological Themes Shaping the 2025 Awards

The 2025 Taiwan Future Technology Awards celebrate a diverse range of innovations that embody Taiwan's core research strengths and industrial momentum. Among the 83 award-winning technologies this year, several key themes stand out:

- Artificial Intelligence and Automation: from AI-powered healthcare monitoring systems and autonomous robotics to large-language-model applications in electronic health records and fraud detection.
- Green and Sustainable Energy: including next-generation hydrogen production, carbon-capture materials, and energy-efficient semiconductor technologies for a net-zero future.
- Advanced Semiconductors and Photonics: new 3D-integration platforms, quantum-dot devices, and ultrafast memory architectures that reinforce Taiwan's leadership in the global tech landscape.
- Biomedical and Precision Health Innovations: spanning AI-driven diagnostics, smart surgical systems, and cutting-edge therapeutic platforms such as cell- and extracellular vesicle-based precision therapies.

Spotlight: Targeted Extracellular Vesicles for Liver Repair

Acute liver failure is a life-threatening condition with few effective treatments. Scientists in Taiwan have recently developed a smart strategy to deliver healing molecules precisely to damaged liver cells — using tiny natural messengers called extracellular vesicles (EVs).

EVs are nano-sized bubbles secreted by cells that carry proteins and genetic material to help other cells communicate. They can serve as natural delivery vehicles, yet a major challenge remains: conventional EVs tend to diffuse throughout the body, making it difficult to reach the right target.

A research team in Taiwan overcame this hurdle through an elegant chemical approach known as click chemistry. They attached a small antibody fragment onto the EV surface, enabling it to recognize and "dock" onto liver cells. These engineered vesicles, termed CAR-sEVs (Chimeric Antigen Receptor small Extracellular Vesicles), home precisely to liver tissue [2].

When tested in mice with severe liver injury, CAR-sEVs accumulated efficiently at the damaged site, reduced inflammation, and promoted tissue regeneration. Compared with unmodified EVs, these targeted vesicles demonstrated stronger localization and superior therapeutic outcomes — all without using live cells, thereby minimizing safety risks.

This innovation represents more than a single therapy. Because the targeting ligand can be modified to recognize different tissues, the same platform could one day deliver treatment to the heart, brain, or even tumors. It is a flexible, modular system that embodies the spirit of precision medicine.

From Targeting to Transformation

For Taiwan, this breakthrough exemplifies how biotechnology, chemistry, and medicine can converge to create next-generation, cell-free therapies. The development of targeted EVs not only pushes the frontiers of precision medicine but also echoes the vision of the 2025 Taiwan Future Technology Awards to transform scientific excellence into practical innovations that improve human health and quality of life.

In essence, targeting turns EVs from mere biological messengers into guided therapeutic couriers. It captures the core of what future technology stands for: innovation with purpose, precision, and real-world impact.

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IMAGE FROM CANVA.COM

Overview and Recommendations on Taiwan's Exosome Market: EVs/exosome Definitions, Analytical Methods, and Application Scope

Introduction: Exosomes as an Emerging Hotspot amid Market Chaos

Since the 1990s, extracellular vesicles (EVs) were discovered to play immunological roles and to potentially mediate intercellular communication, which sparked a surge of related research [1]–[3]. In 2013, Rothman, Schekman, and Südhof were awarded the Nobel Prize in Physiology or Medicine for their work on the molecular mechanisms of vesicular trafficking, which indirectly raised global attention on EVs/exosomes [4]. Subsequencely resources and investments into this field rapidly expanded.

Nevertheless, our understanding of EVs and exosomes remains limited. The International Society for Extracellular Vesicles (ISEV), founded in 2011, has updated its minimal information guidelines three times within a short period. MISEV2014 defined EVs and introduced the "three positive/one negative" protein characterization baseline [5]. MISEV2018 emphasized the unified terminology "EVs" and recommended enhanced methodological reporting [6], while MISEV2023 further incorporated advanced approaches, multimodal characterization, and reproducibility [7], [8].

Despite such rigor, commercial forces have advanced more quickly than science or regulation. In recent years, exosomes have rapidly risen in both medical and cosmetic markets, being branded as a "next-generation cell therapy." In Taiwan, the pace of commercialization has far outstripped the maturity of scientific and regulatory frameworks, leading to a proliferation of heterogeneous products, exaggerated claims, and lack of testing standards.

In May 2025, the Taiwan Food and Drug Administration (TFDA) convened a workshop on exosome-related products, signaling regulatory agencies' intention to intervene and restore market order.

This article therefore proposes, based on MISEV2023, a feasible framework for exosome product testing standards as a reference for academia, industry, and regulators.

I. Definitions and Classification: The International Consensus of MISEV2023

According to the latest ISEV guidelines (MISEV2023), exosomes should be considered within the broader category of EVs, and standardized terminology/classification is critical for both research and regulation [7], [8].

- **Unified definition:** Unless the subcellular origin is clearly demonstrated (e.g., multivesicular body release), terms like "exosome" or "microvesicle" should be avoided; the general term "EVs" is preferred.
- **Classification:** Based on size (e.g., small EVs < 200 nm), origin (cell type), and biochemical markers (CD9, CD63, TSG101), among other descriptors.
- **New concepts:** MISEV2023 also introduces "extracellular particles (EPs)" and "non-vesicular extracellular particles (NVEPs)," reflecting a more nuanced understanding of extracellular components [7], [8].

Youlin Wu
Co-Founder, Prosperity Bio Co., Ltd., Taiwan
PhD Candidate, Institute of Chemical Engineering, National Taipei University of Technology

Youlin Wu is the co-founder of Prosperity Bio Co., Ltd., where he works at the intersection of extracellular vesicles (EVs), RNA-related technologies, and translational biotechnology. His professional focus includes supply-chain development, quality and analytical standards, and market strategy for advanced biotherapeutic platforms. In parallel, he is pursuing a PhD in Chemical Engineering at National Taipei University of Technology, Taiwan, with research interests spanning EV characterization, analytical methodologies, and clinical-adjacent applications.

II. Analytical Methods: Imaging, Quantification, and Functional Assays

Testing methods for exosomes/EVs encompass purity, particle size, surface markers, and biological activity. Among these, imaging remains both critical and underdeveloped [10], [11].

1. Imaging methods:

- **TEM/SEM:** Direct visualization of morphology and size distribution (qualitative).
- **Confocal microscopy with labeling:** Detects specific markers.
- **Fluorescent nanoparticle tracking analysis (NTA):** Quantitative analysis of EV subtypes.
- **Super-resolution microscopy (STORM, SIM, STED):** Overcomes diffraction limits for precise molecular localization.
- **Cryo-EM:** High-resolution structural visualization.

2. Particle size and concentration:

- **NTA:** Widely used standard for size and concentration.
- **DLS:** Useful for homogeneous samples, less reliable for heterogeneous EVs.

3. Biochemical analysis:

- Western blot/ELISA for EV markers (CD63, TSG101).
- Flow cytometry with nanoparticle platforms for quantitative assessment.

4. Functional assays:

- Uptake and target-cell assays (migration, differentiation, immune responses).

III. Clinical Applications and Challenges: Promising but Immature

According to Nature Reviews Drug Discovery and the Journal of Extracellular Vesicles, as of September 2025, no exosome products have received formal drug approval from the U.S. FDA or the EMA [12]. The FDA has repeatedly stated that "there are currently no FDA-approved exosome products" and issued warnings against unlawful marketing [13], [14]. In the EU, clinical trial approvals and ATMP/orphan designations exist but do not yet constitute market authorization [19]–[22].

Ongoing investigational new drug (IND) trials focus on:
- Regenerative medicine (skin, cartilage repair)
- Immune modulation (autoimmune diseases)
- Oncology (adjunctive therapy)
- Neurodegenerative disease models

Most evidence of efficacy still stems from preclinical animal models. Mechanisms (e.g., RNA cargo, source-cell specificity) remain under debate, and consensus has not been reached [6]–[8].

IV. Taiwan Market Status: Urgent Need for Regulation and Standards

Products labeled with "exosomes" in Taiwan mainly include:
- Cosmetics/skincare: Often without concentration/source labeling.
- Medical devices with injectable solutions: Sometimes derived from stem cell culture supernatants.
- Health supplements: Largely marketing-driven, lacking scientific validation.

Most lack GMP-grade manufacturing, standardized quality control, or validated assays, undermining both consumer trust and industry credibility.

V. Recommendations and Outlook

1. For regulators:

- Establish definition and testing standards for exosome products (e.g., size, markers, purity based on MISEV2023).
- Implement tiered regulation (cosmetic vs. medical device vs. therapeutic).

2. For industry:

- Select partners with validated EV sources and GMP-compliant manufacturing.
- Track TFDA/ICH regulatory updates and invest in lab-level QC capacity.
- Join ISEV and other standardization groups for technical support.

3. For researchers:

- Employ multimodal validation (imaging, functional, molecular).
- Focus on translational models with potential for early clinical entry.

Conclusion

The exosome market is booming, yet exosomes remain highly heterogeneous and incompletely understood. Without clear testing standards and regulatory systems, sustainable development will be difficult. Taiwan should seize this critical moment to establish comprehensive and credible industry norms through joint efforts across academia, industry, and government.

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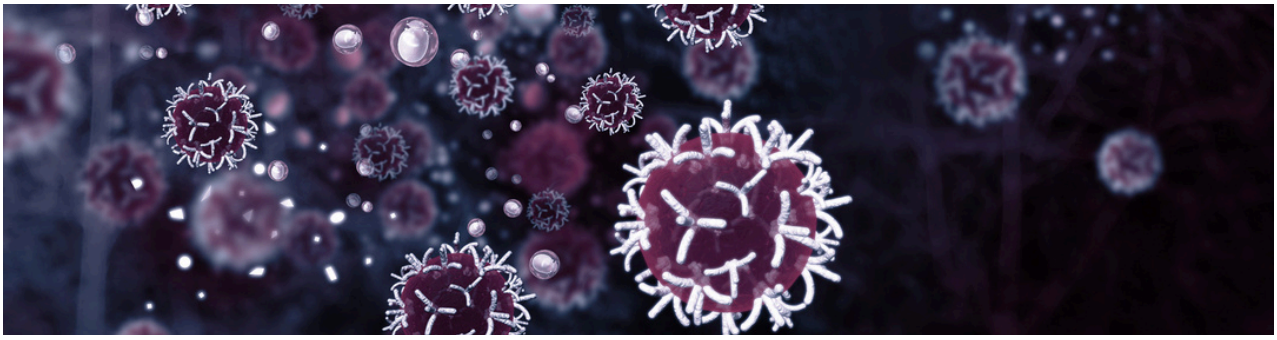

IMAGE FROM CANVA.COM

Gwo Xi's stem cell product GXNPC1® shows safety and beneficial effect for stroke patients

Abstract

Gwo Xi Stem Cell Applied Technology Co., Ltd. (hereinafter "Gwo Xi") is a Taiwan-based cell therapy company committed to developing stem cell medicines that address unmet medical needs. One of its key targets, chronic ischemic stroke, is among the most challenging neurological disorders, often leading to long-term disabilities and limited therapeutic options. Gwo Xi's GXNPC1®, an autologous adipose-derived stem cell (ADSC) therapy, is designed to promote neurovascular repair, angiogenesis, and functional recovery, offering a promising regenerative approach for patients suffering from chronic ischemic stroke. Preclinical and IND clinical studies have demonstrated that GXNPC1®exerts potent regenerative effects through angiogenesis, immunomodulation, and neuronal differentiation. Phase I and II trials conducted in Taiwan confirmed its safety profile and revealed consistent improvements in National Institutes of Health Stroke Scale (NIHSS). Through intracerebral administration, GXNPC1® can directly target ischemic brain regionsto enlarge infiltrated cells to take effect. GXNPC1® is currently advancing toward Phase III clinical trial. With Taiwan's recent enactment of the Regenerative Medicine Act (RMA) and the Regenerative Medicinal Products Act (RMPA)(collectively referred to as the "Regenerative Medicine Dual Legislation"), GXNPC1® has completed Phase II clinical trials. The release of new laws will accelerate the commercialization of regenerative therapy products. GXNPC1® is expected to revolutionize the current treatment model for chronic ischemic stroke in Taiwan.

Keywords: Gwo Xi, stem cell, GXNPC1®, chronic stroke, autologous, adipose, intracerebral injection, regenerative medicine.

Introduction

Chronic stroke remains one of the leading causes of long-term disability worldwide. Although thrombolysis and thrombectomy have revolutionized acute stroke management, their benefits are confined to a narrow therapeutic window(≦24 h), resulting in most patients progressing into the chronic stage with persistent motor, sensory, and cognitive impairments [1,2]. During this late phase, glial scarring, neuroinflammation, and synaptic disconnection severely restrict neuroplasticity and limit the capacity for functional and activity recovery. Consequently, there is an urgent need for therapeutic strategies that can actively promote neural regeneration, vascular remodeling, and reorganization of motor networks in chronic stroke patients.

Stem cell therapy has emerged as a promising approach to address these challenges [3,4,5]. Among various stem cell sources, adipose-derived mesenchymal stem cells (ADSCs) are particularly attractive due to their advantages, including ease of harvest, multilineage differentiation potential, and strong secretion of trophic and angiogenic factors [3,6]. GXNPC1®, developed by Gwo Xi, is an autologous ADSC-based therapy designed to restore neurological function and coordination in patients with chronic stroke through proprietary cell culture technology.
This article reviews the preclinical evidence, clinical outcomes, and mechanistic rationale of GXNPC1®, highlighting its therapeutic innovation in chronic stroke rehabilitation and its ongoing development toward Phase III clinical trial under RMPA in Taiwan.

Preclinical Basis & Experimental Evidence

GXNPC1® utilizes autologous adipose-derived stem cells (ADSCs) harvested from 3-5 grams of each patients' adipose tissue and processed under Good Manufacturing Practice (GMP) standards to ensure quality, sterility, and reproducibility. Extensive preclinical studies have demonstrated the therapeutic potential of ADSCs in chronic ischemic stroke models. In thromboembolic stroke models, ADSC transplantation significantly enhanced post-stroke behavioral recovery and mitigated cortical neuronal apoptosis, indicating neuroprotective and restorative effects [7,9].

Importantly, these studies confirmed a favorable safety profile, with no evidence of tumorigenicity or abnormal cell proliferation. The functional gains observed in animal models were sustained over several weeks to months, indicating durable benefits beyond transient trophic effects.

These preclinical data provided the foundational evidence for the clinical translation of GXNPC1®, supporting its capacity to enhance recovery in chronic stroke by improving local perfusion and promoting tissue remodeling. The results also validated the feasibility of intracerebral injection as a route of administration (ROA).

Clinical Translation and Trial Evidence

The first-in-human Phase I trial (NCT02813512) was conducted in Taiwan by Dr. Lin, Shinn-Zong, involving three chronic stroke patients with stable deficits persisting for over six months. Each participant received a intracerebral injection of 1×10^8 autologous ADSCs within 1 mL. The procedure was well tolerated, with no severe adverse events or suspected unexpected serious adverse reactions (SUSARs) observed during six months of follow-up. MRI scans showed localized signal alterations near the tranplantation tract, indicating tissue remodeling or possible graft survival. Functionally, participants improved by 5–15 points on the National Institute of Health Stroke Scale (NIHSS), 25–50 points on the Barthel Index, and up to 21 points on the Berg Balance Scale [8]. These improvements suggest meaningful recovery in a population typically resistant to spontaneous improvement.
Subsequently, Phase II (NCT04088149) study expanded patient enrollment, with data showing continued safety and measurable clinical benefits. The high-dose cohort achieved an average NIHSS improvement of 2.7 points by 24 weeks, and 89% of participants exhibited improved behavioral and functional metrics. Currently, GXNPC1® has applied for Phase III clinical trials and, under Taiwan Regenerative Medicinal Products Act, has the potential to receive a 5-year conditional approval to be marketed in advance.

GXNPC1®, *a novel autologous adipose-derived stem cell therapy for treating chronic stroke, focusing on angiogenesis, neural differentiation, and motor function improvement.*

Therapeutic Administration & Precision Administration

A defining feature of GXNPC1® lies in its precise administration. Unlike intravenous or intrathecal stem cell infusions, GXNPC1® is administered directly into the brain via stereotactic guidance. This approach ensures localized cell distribution within peri-infarct regions, maximizing regenerative impact while minimizing systemic exposure. Such precision administration represents a major advancement in cell-based therapeutics, aligning with the principles of personalized medicine and targeted neurosurgical delivery.

Comparative Advantage & Innovation

GXNPC1® distinguishes itself through several technological and clinical advantages: (1) It is an autologous, patient-specific therapy with minimal immunogenic risk; (2) It leverages a well-established ADSC processes, providing qualified cell dosage under GMP standards; (3) Its paracrine and exosomal signaling provide multi-dimensional repair; and (4) It has achieved advanced clinical development, with a Phase III application underway. The therapy has been recognized with innovation awards from Taiwan's healthcare and biotech agencies, reflecting confidence in its translational and commercial potential.

Challenge & Future Perspectives

Despite the promising clinical outcomes observed with GXNPC1®, several challenges must be addressed to enable its routine application for chronic stroke rehabilitation. Firstly, autologous cell therapy requires individualized manufacturing. The overall cycle is complex and involves multiple stages. This limits scalability.

Gwo Xi's strategy is to simplify the treatment process through modular processes: for example, introducing standardized cell cryopreservation and In-Process Control (IPC) to shorten turnaround time, reduce patient waiting times and reduce center pressure.

Meanwhile, optimizing administration strategies, such as cell dosage escalation, and timing relative to stroke onset, will be critical to enhance efficacy [10]. Establishing solid clinical biomarkers to monitor response, along with standardized functional assessment scales, will facilitate individualized treatment planning. Moreover, integration of advanced imaging techniques, including MRI-based perfusion mapping and diffusion tensor imaging, can provide objective evidence of structural and functional improvement in neural circuits.

Finally, expanding the manufacturing and quality control framework for ADSC processes fitting GMP standards will be essential to ensure consistent product quality. Addressing these translational and operational challenges will be pivotal for GXNPC1® to achieve broad clinical adoption and fulfill its potential as a promising stem cell therapy for patients with chronic stroke.

Conclusion

GXNPC1® represents a scientifically grounded and clinically validated regenerative therapy that integrates angiogenesis, neurogenesis, and immunomodulation to address chronic ischemic stroke. Its strong safety record, measurable functional benefits, and advancement to Phase III trials mark it as a frontrunner in the field of regenerative neurology. By combining precision delivery with the intrinsic repair capabilities of ADSCs, Gwo Xi's GXNPC1® offers renewed hope for patients facing long-term disability after stroke and sets a benchmark for future neurodegenerative therapies.

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In Loving Memory of
Prof. Yao Chang Chen

CONDOLENCE LETTERS FROM ACTO MEMBERS

Dear Dr. Shimosaka,
I was deeply saddened to learn of Professor Yao Chang Chen's passing.
Whenever I met Professor Yao Chang Chen at ACTO meeting, he always spoke to me warmly and informally. I have particularly vivid memories of the ACTO 2013 annual meeting, during which he served as President. The commemorative plaque from that time is still displayed in my office. It feels as though our society has lost someone truly irreplaceable.
Please accept my deepest condolences, and I sincerely pray that Professor Yao Chang Chen may rest in peace.

Best regards,
Emeritous Prof. Keiya Ozawa,
Jichi Medical University, ACTO Board Member

Dear Sam,
Thank you very much for letting me know. This is really very sad news.
Prof Yao Chan Chen was a remarkable and gifted person and has been able to make several careers at the highest level, combining his work as a leading hematologist with that of a famous writer. Only few weeks ago, I received a copy of his book "A tale of three tribes in Dutch Formosa" that was published just one year ago. It is a demonstration of his versatility. He was also a very kind and gentle person with compassion for his patients. He will be deeply missed but many dear memories will remain. My deepest sympathies to his family and friends.

Best wishes,
Prof. Willem Fibbe,
Leiden University, Former EHA President
Editor-in-Chief Blood ICT

Dear ACTO Member,
Thank you for sharing this difficult news. I was deeply saddened to learn of Professor Chen's passing. Please accept my sincerest condolences during this very challenging time. I understand the profound impact his contributions have had.
We will certainly keep his memory in high regard. May he rest in peace.

Ho Chi Min BTH Hospital,
ACTO Committee member

In Loving Memory of
Prof. Yao Chang Chen

CONDOLENCE LETTERS FROM ACTO MEMBERS

Thanks for letting us know Sam
I have fond memories of Prof Yao Chan Chen and have known him at the start of ACTO and before that APBMT. We would see each other too also at ASH and EBMT. A softly spoken man and a true gentleman. My deepest condolences go to his family and friends.

Best wishes
Prof. Mickey Koh,
Prof. St. George Hospital, London and Singapore HSA Director
Vice President of ACTO

Hi Sam
So sorry to hear of that news. Very important person indeed. And I know you were close friends. Lauren and I send our condolences

Kenneth Kaushansky MD, MACP
Dean and Professor Emeritus
Renaissance School of Medicine
Stony Brook University
Former President of ASH and Editor-in-Chief for Blood

Dear Sam,
Thank you for informing me of Professor Yao Chan Chen's passing.
This is deeply saddening. He was a pivotal figure in ACTO's activities, and his contributions to the field were immense. He will be greatly missed. I extend my sincere condolences to his family, friends, and colleagues. May his soul rest in eternal peace.

Ferry Sandra
Vice President of ACTO Indonesia

Dear Sam,
Acknowledge your message. Dr. Chen is a friend of more than 30 years who has made great contributions to TW medicine, in particular, haematology field.

Dr. 賴博雄
Taiwan Researcher worked for Amgen when we developed EPO
and G-CSF. He analyzed amino acid sequence of EPO and G-CSF

In Loving Memory of
Prof. Yao Chang Chen

CONDOLENCE LETTERS FROM ACTO MEMBERS

Dear Dr. Shimosaka and all members of ACTO

It brings us so incredible sorrow, heartbreak, and a deep sense of emptiness. When we met recently in Taiwan, he was still full of energy-introducing his newly written book, asking warmly about many long-standing colleagues and scholars in Korea, and showing unchanged enthusiasm for academic pursuits. It is truly hard to believe that he has left us so suddenly.
I know that he devoted himself not only to the field of HSCT and cellular therapy in Taiwan, but also to the advancement of these disciplines throughout the entire Asia-Pacific region.
We honor his remarkable achievements and lifelong dedication, and we sincerely pray that he may rest in eternal peace in heaven!

Hee-Je Kim,
Prof. of Catholic Medical University, Seoul, ACTO VP

Dear Professor Shimosaka,
This is truly a very sad news.
Prof. Yao-Chan Chen made tremendous contributions throughout his life. As the founder of TACT (Taiwan Association for Cellular Therapy), he actively advanced our activities and development. He also contributed greatly to ACTO's initiatives. He was a pioneer of bone marrow transplantation. He was not only an outstanding physician to his patients but also a remarkable author whose works on Taiwan's history have had a lasting impact.
His passing is truly a great loss. My deepest condolences go to his family and friends.
May he rest in peace.

Sincerely,
Wannhsin Chen

Dear Sam,
Dear ACTO Members,
This is truly sad news about the loss of a great personality and a dedicated, contributing ACTO member, Professor Yao Chan Chen. I remember his active involvement during the ACTO meeting in Taiwan, as well as his endless care and kindness. I feel deep sorrow at his passing.

Sincerely
Prof. Abbas Ghaderi,
Shiraz Institute for Cancer Research, ACTO VP
Iran

In Loving Memory of
Prof. Yao Chang Chen

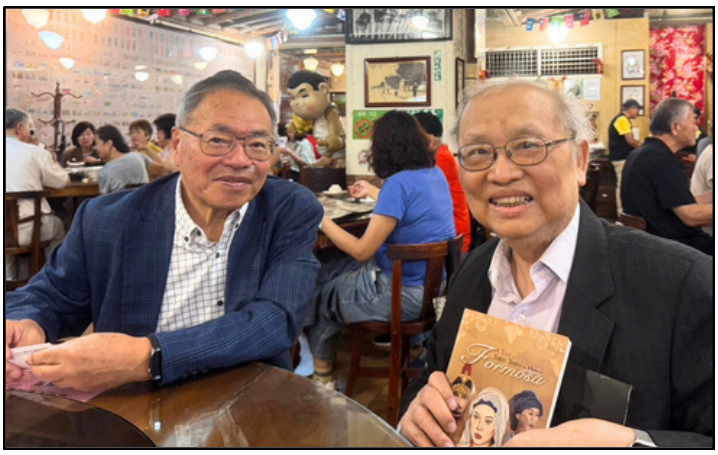
CONDOLENCE LETTERS FROM ACTO MEMBERS

Dear Sam
This is very sad news. He contributed to ACTO activities and it's a big loss to the field.
I still remember his kind smile and great help while I last visited Taiwan.
My deepest condolences go to his family and friends. May him rest in peace.

Saeng Prof. Saengsuree Jootar,
Mahidol University, Bangkok, ACTO VP Thailand

Dear Sam,
This is truly sad news. Prof. Yao Chan Chen was a significant contributor to ACTO activities and a real loss to the field. My sincere condolences go out to his family and friends.
May his soul rest in peace. Thank you for sharing this information.

Srinivasan N Kellathur, PhD
Pharma Technical Regulatory Policy, APAC
Roche Singapore
Former director for cell therapy, HSA Singapore,
Chair for Industry Committee, ACTO



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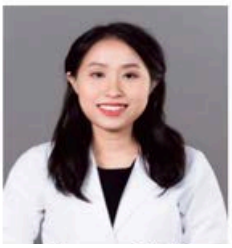

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