The ACTO Times

Asian Cellular Therapy Organization

VOL. 02
ISSUE 03

The 16th ACTO Annual Congress & APSEV 2025 Spotlight

Academic Highlight
Circadian Rhythm, Skin Cancer Stem Cell, Tumor Microenvironment, Extracellular Vesicles-Exosomes

Updates of CGT Regulation
Singapore

2025 SUMMER EDITION

The ACTO Times
Asian Cellular Therapy Organization
2025 SUMMER EDITION

CONTENTS

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

Greetings
The ACTO Chairperson

Dear ACTO members,

We are glad to share the Summer 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 all over Asia, ACTO serves for peoples in Asian as well as those in other countries who need CGT.

Since our first meeting in Japan, led by Dr. Yoichi Takaue in 2010, 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. Now we are happy to invite Indonesia to be a key member country for the operation of ACTO who will organize the 17th ACTO Annual Meeting in 2026.

Today many countries in Asia introduced new regulation for CGT. Regulator agency members are directly participating ACTO activities and can exchange information freely. It is important for academy, industry and regulatory agency to work together for the development of CGT. ACTO will take responsibility to share the correct, precises information related to CGT. We started 'The ACTO Times', led by Editor-in-Chief Distinguished Prof. Rita Yen-Hua Huang of Taipei Medical University, for this purpose. Prof. Huang has made remarkable contributions by publishing the five editions (Spring, Summer, and Autumn, 2025 New Year and Spring), gathering updates from 15 Asian territories on advanced cell and gene therapy (CGT) from regulatory and industry committees.

Now we are ready for the 16th ACTO Annual Meeting, August 14~16, 2025 in Singapore. 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.

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.

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,

I am excited to present the 2025 Summer Edition of The ACTO Times, which highlights the upcoming 2025 Singapore ACTO Annual Meeting and recent advances in Asian cell and gene therapy (CGT). As of 2025, over 100 CGT products have been approved globally, yet no exosome product has received global approval. The US FDA and EMA continue to lead in CGT product approvals, while Asia is experiencing rapid growth, particularly in the CGT market, clinical trials, and exosome development.

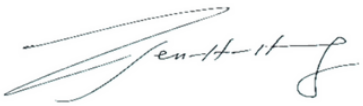
Under the leadership of Chairperson Dr. Shimosaka and with the dedicated efforts of the ACTO committee, ACTO has played a pivotal role in advancing precision CGT within Asian regions. In 2024, ACTO launched its official magazine, The ACTO Times, to share the latest developments in global CGT, including translational medicine, regulation, clinical trials, and industry insights. To date, The ACTO Times has published six editions spotlighting global CGT advances and developments in Asian territories.

In this Summer Edition, we spotlight the Singapore ACTO Annual Meeting and highlight recent advances in EV translational medicine. Importantly, we have new established an "Academic Zone" to foster the development of academic translational medicine in future CGT.

We warmly invite you to join the 2025 ACTO Annual Meeting in Singapore this year. This event will bring together experts and leaders in the field to discuss the latest advancements and future directions in cell and gene therapy.

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

Sincerely,



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

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

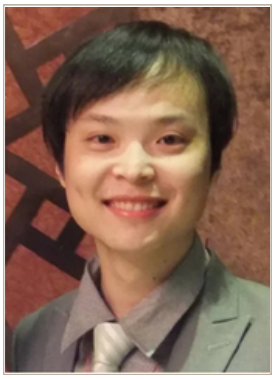
Artit Ungkanont, Bangkok
Kazuto Takesako, Shiga
Kunihiko Suzuki, Tokyo
Hirokazu Takazawa, Beijing

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 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
Madurai

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

Tony Yu-Xiu Lin, MS
Taipei

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

UNVEILING THE TIMELESS TAPESTRY

THE CHRONICLE OF ACTO THROUGH TIME

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

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

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

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

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

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

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

PRELUDE

NAVIGATING THE UNIQUE DYNAMICS OF CGT IN ASIA

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

Large Population Dynamics

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

Gene Background Diversity

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

Culture-Related Pre-Clinical Research

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

.

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

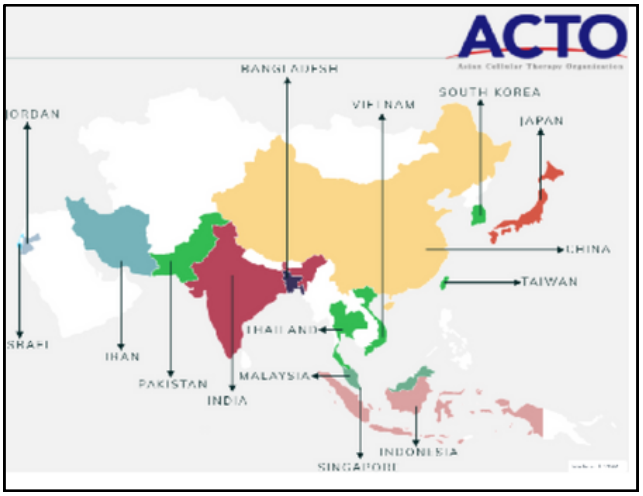
Over the years, the ACTO meetings became a cornerstone for professionals in the field, providing a platform for networking, sharing knowledge, and forging international partnerships. As the organization evolved, reflecting the dynamic landscape of CGT in the Asia-Pacific region.

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.



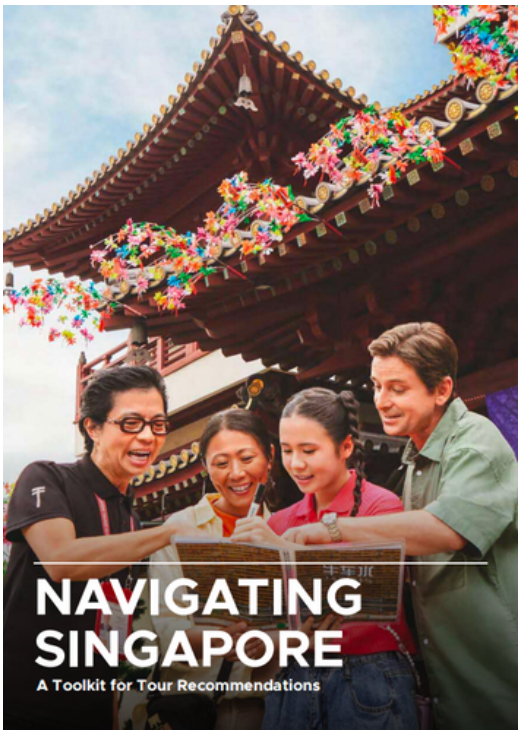
As of the present moment, the Asian Cellular Therapy Organization (ACTO) has seen the enthusiastic engagement of 15 regional territories in its annual meetings. This collective involvement underscores the organization's commitment to fostering collaboration and knowledge exchange among diverse regions 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.

Preface 2025 ACTO Annual Congress in Singapore

PROFESSOR MICKEY B C KOH

It is with immense pleasure that I welcome all invited speakers, delegates and honoured guests to the 2025 Asian Cellular Therapy Organisation (ACTO) congress held in Singapore. This congress is happening at a pivotal moment in the fast-evolving field of cell and gene therapy. There are bewilderingly rapid developments in diverse areas from approved gene therapy in congenital diseases like haemoglobinopathies to the increasingly upfront use of CAR-T cells in B cell malignancies and extending into non malignant diseases like autoimmunity. Equally, progress is being seen with the use of stem cells in tissue repair and regeneration as well as the ancillary manufacturing advances that underpin the therapeutic quality of these cellular products.

ACTO is unique in its commitment to focus on the entirety of the landscape for cell and gene therapy in Asia. I have been involved with ACTO from its formation and have witnessed the increasing prominence of Asia in this field. China is a world leader in CAR-T development and clinical trials while Japan has invested significantly into induced pluripotent stem cell (iPSC) technology stemming from its recent Nobel prize winning discovery by Yamanaka. This revolutionary potential of cell and gene therapy is being recognised by many governments in Asia as a game changer, certainly in Singapore too with enthusiasm for helping to nurture home grown cell therapy companies and building an ecosystem from science to training, manufacture and regulation. The result would of course be the promise of substantial medical and economic benefit.



www.stb.gov.sg

This annual meeting will bring a diverse group of speakers, guests and participants. There is intentionally a focus on regulatory issues, again unique to ACTO and recognising the urgent need for harmonisation in Asia. In addition, we encourage the active participation of Asian cell and gene therapy companies to facilitate a dialogue between science, manufacturing, clinical indications, safety and regulations.

I would like to thank the local organising committee who have done most of the work. The committee hopes that your time spent in Singapore will be a scientifically stimulating one, that you will forge collaborative opportunities with other attendees in this meeting and I hope you also find some time to enjoy Singapore- a safe, modern and beautiful city state with many world class attractions and a passion for food and eating that is second to none.

Thank you for attending and contributing to this meeting.

Professor Mickey B C KOH

APSEV 2025 Spotlight

Hsing, Jiu-Chen
Taipei Medical University

Illuminating the Next Frontier in Regenerative Nanomedicine

The 2025 APSEV International Conference, held in Singapore, spotlighted major breakthroughs at the frontier of regenerative nanomedicine. As a leading event in Asia devoted to extracellular vesicle (EV) research, APSEV provided key insights into how these vesicles—particularly engineered cell-derived nanovesicles (CDNs)—are transitioning from being seen as passive cellular debris to becoming advanced therapeutic tools. With growing relevance in tissue repair, oncology, and regenerative medicine, EVs are now redefining precision therapy in modern medicine.

The era of engineered CDNs has arrived

A significant aspect of the presentation was the emergence of engineered cell-derived nanovesicles (CDNs) as versatile carriers capable of delivering RNA, proteins, and therapeutic agents with high specificity. Rather than remaining purely theoretical, methodologies such as membrane remodeling, modulation of vesicle permeability, and optimization of miRNA payloads have been effectively translated into reproducible experimental protocols. Notably, CDNs loaded with specific microRNAs exhibited considerable cytoprotective effects, particularly in reducing oxidative stress and preventing cell death in injury models. These results highlight a pivotal shift within the field, transforming extracellular vesicles (EVs) from passive biological byproducts into purposefully designed, bioactive delivery systems.

From "Delivery Vehicle" to "Targeted Navigator"

What truly marked a leap forward was the integration of peptide-guided delivery strategies along with click chemistry. One prominent study showed cDNA functionalized using IMTP or Ischemic Myocardium-Targeting Peptide.

These bioconjugation reactions were used for performing the functionalization without copper. Researchers used Ac4ManNAz-based metabolic labeling; in addition, they then used SPAAC (strain-promoted azide-alkyne cycloaddition); through this, researchers precisely presented IMTP on cDNA plus did not compromise vesicle integrity or function. This bioengineering approach enabled cDNA for homing in on infarcted heart tissue because it demonstrated improved biodistribution as well as therapeutic localization in vivo. Such targeted delivery minimizes off-target effects plus unlocks a new modular platform applicable for disease-specific uses, setting the stage for next-generation precision nanomedicine.

A Reflective Parallel—miR-24-3p in the Ovary and Heart

Among all of the sessions, one presentation showed that miR-24-3p protects the heart in a deep way for me. The mechanism is similar to my own findings within a chemotherapy-induced POI model. MiR-24-3p suppresses Keap1 to activate the Nrf2/ARE antioxidant pathway, also this likewise reduces oxidative damage and cell death in ovarian tissue.

We may be able to achieve localized non-hormonal regenerative treatment of POI and related reproductive disorders if cDNAs engineered for cardiac repair can be retargeted to ovarian tissue perhaps using follicle-homing peptides or zona pellucida-binding ligands this convergence of evidence suggests a compelling translational pathway.

Translational Potential in Regenerative Medicine

The successful demonstration of miRNA-engineered CDNs for cardiac repair has drawn increasing attention to how they could translate across systems. Gynecological disorders such as chemotherapy-induced primary ovarian insufficiency (POI) and circadian dysregulation do present one of the most compelling possibilities in this area. In much the same way as myocardial tissues do, the ovaries suffer from oxidative stress, and mitochondrial dysfunction, and also apoptosis after chemotherapeutic exposure occurs in them. For ovarian repair at specific sites, clinically approved therapies are lacking. This delivery system that is CDN-based could be adapted now for reproductive applications. That approach makes focused ovary renewal feasible. CDNs improved by miR-24-3p could target ovarian tissues precisely. This occurs when ovarian-specific peptides or follicle-homing ligands are used along with being combined with click chemistry. For women of reproductive age and women who are menopausal, such a strategy holds promise for the addressing of hormone regulation, for circadian health, and for fertility preservation.

Toward a Modular Therapeutic Platform

One overarching trend from the APSEV conference was that CDNs do envision an evolution of single-solution therapy into a customizable modular platform. Researchers presented the potential for reconfiguring CDNs through interchangeable modules tailored to address specific diseases. These modules included surface ligands intended for targeting, miRNA/protein payloads meant for function, and membrane engineering designed for circulation time in myocardial infarction, ovarian dysfunction, neurodegeneration, and so on. AI-guided drug discovery along with personalized medicine pipelines are set to integrate into this plug-and-play platform concept. CDNs also have more tissue affinity, are more flexible to manufacture, and are more immune compatible, compared to lipid nanoparticles (LNPs) or viral vectors, so systemic therapies have a more viable long-term option.

Challenges in Clinical Translation

Despite these promising developments, engineered CDNs face several important barriers prior their clinical translation.

socrates-singapore.org/apsev-2025/

First, there are challenges to scaling up production. The current CDN isolation and purification methods are based on lab-scale ultracentrifugation, microfiltration and they have yet to be adjusted for GMP manufacture. Secondly, the immune response and long-term stability of these targeting peptides require careful attention to determine if they are safe for in vivo applications. Furthermore, the absence of standardized biodistribution and delivery efficiency metrics is a regulatory challenge and also precludes cross-study comparisons.

These are issue that underline the necessity of a more effective interdisciplinary cooperation between material scientists, pharmacologists and clinician. However, as evidenced throughout the multiple presentations at APSEV 2025 (and those presented in this special issue), these hurdles do not hinder scientific progress but instead promote innovation, speed translational research and advance EV-based technologies towards realization into clinical practice.

Conclusion

A New Era at the Nano–Cellular Interface

As the frontiers of regenerative biology, nanotechnology and molecular targeting blur into each other, cell-derived nanovesicles (CDNs) are increasingly being viewed not as tools per se but rather repurposable platforms capable of bending traditional therapeutic design rules. The advances in technologies available at APSEV 2025, including miRNA-loaded vesicles and click chemistry-based targeting of Bioorthogonal chemistry are indicative for more than incremental progress. They constitute a conceptual revolution to the concept of programmable, organ-specific and patient-responsive therapies. The lesson here, whether the goal is to understand biomolecular structure or treat diseases: The future of precision medicine may not be contained in just synthetic drugs developed through reductionist principles, but might instead come from re-engineered biological messengers extracted directly from our cells. And every time such a vesicle is engineered, we are that much closer to being able to live in a world where healing can be not only targeted but smartly mobilized.

Supplementary documents

[1] Lv, Qingbo, et al. "Nanosponge for iron chelation and efflux: a ferroptosis-inhibiting approach for myocardial infarction therapy." Advanced science 11.25 (2024): 2305895.
[2] Ngo, Vy, and Martin L. Duennwald. "Nrf2 and oxidative stress: a general overview of mechanisms and implications in human disease." Antioxidants 11.12 (2022): 2345.

Updates on CGT Regulation

Eddie Tan[1], Mickey BC Koh[2]

1. Centre of Regulatory Excellence, Duke-NUS Medical School, National University of Singapore
2. City St Georges, University of London, UK and St George's University Hospital, London, UK

IMAGE FROM CANVA.COM

Current Landscape of Cell and Gene Therapy in Singapore

Singapore has emerged as a key player in the cell and gene therapy (CGT) sector in Asia, with significant developments in infrastructure, regulatory frameworks, and clinical advancements. The country has strategically positioned itself to become a regional hub for CGT research, development, and clinical applications through substantial investments, purpose-built facilities, and collaborative ecosystems.

Regulatory Framework and Government Support

Risk-Based Regulatory Approach for Cell, Tissue, and Gene Therapy Products

The Health Sciences Authority (HSA) of Singapore implemented a fit-for-purpose regulatory framework for Cell, Tissue, and Gene Therapy Products (CTGTPs) on March 1, 2021 (https://www.hsa.gov.sg/ctgtp/regulatory-overview).

Under this framework, CTGTPs are stratified into lower-risk Class 1 CTGTP or moderate-to-higher-risk Class 2 CTGTP based on their degree of manipulation, intended use, and whether they are combined with therapeutic products or medical devices.

This risk-based regulatory approach aims to facilitate successful product development and registration in Singapore for innovative CTGTPs while ensuring reasonable safeguards on the safety, quality, and efficacy of the products.

(https://pubmed.ncbi.nlm.nih.gov/37526849/).

The approach is designed to be least burdensome while maintaining appropriate oversight, which is essential for promoting innovation in this rapidly evolving field.

In-house manufacturing regulated by the Healthcare Services Act

Singapore has established specific licensing conditions for healthcare institutions that administer cell, tissue, and gene therapy products (CTGTPs) manufactured in-house under the Healthcare Services Act 2020. These conditions apply to acute hospitals, outpatient dental services, and medical services. They cover CTGTPs made from autologous or allogeneic human cells/tissue, animal cells/tissues, or recombinant nucleic acids.

In-house CTGTPs can only be used in generally accepted treatments, approved research or clinical trials, or innovative salvage therapy. Before administration, patients must be informed about the intervention's purpose, the CTGTP's in-house manufacturing, the method, potential outcomes, registration status, benefits, risks, and costs. Licensees must have systems for managing adverse events, long-term follow-ups, and CTGTP traceability. They must notify the Ministry of Health (MOH) about manufacturing, seek necessary approvals, and report serious adverse events. Additionally, they are required to submit patient data quarterly during the first year, semi-annually in the second year, and annually thereafter.

Governmental Support for CGT

The Singapore government has demonstrated strong support for the CGT sector through substantial investments and strategic initiatives. In 2019, Singapore announced an investment of $80 million to develop core capabilities required for cell therapy manufacturing.

This investment has supported strategic programs addressing major gaps in advanced cellular therapies manufacturing, including scale-up, automation, and cell therapy process development.

Additionally, a task force has been formed by the Ministry of Health (MOH) to develop and support the growing field of precision medicine, including cell and gene therapies

Moreover, the Ministry of Health (MOH) provides subsidies for Cell, Tissue, and Gene Therapy Products (CTGTPs) that have been assessed to be clinically- and cost-effective at Public Healthcare Institutions and included in the CTGTP List. As of August 1, 2024, the CTGTP list includes Tisagenlecleucel (Kymriah), a cell dispersion for infusion. This subsidy framework aims to improve the affordability and accessibility of these advanced therapies for eligible patients.

Infrastructure Development and Manufacturing Capabilities

ACTRIS Facility: A Game-Changer for Singapore's CGT Ecosystem

In August 2023, the Advanced Cell Therapy and Research Institute, Singapore (ACTRIS) opened a new 2,000 sqm cell therapy facility to meet the increasing clinical demand for CGT treatments in Singapore. This replaced the Cell and Gene Therapy Facility (CGTF) at the Health Sciences Authority which was the 1st academic GMP internationally accredited manufacturing centre to provide support for cell and gene therapy trails nationally in Singapore. CGTF was instrumental in initiating the entire cell and gene therapy ecosystem in Singapore and should be credited for its importance in embedding this into Singapore's health system. This new ACTRIS state-of-the-art facility comprises 14 Good Manufacturing Practice-compliant (GMP) clean suites, four translational laboratories, and one quality control laboratory—making it the largest national facility of its kind in Singapore (https://www.cris.sg/news-and-events/media-releases/230804-actris-cell-therapy-facility/)

The facility's advanced infrastructure, including sophisticated air-handling systems, allows ACTRIS to manufacture different cell therapy products concurrently, thereby accelerating patient access to novel treatments1.

The ACTRIS facility supports end-to-end cell therapy process development and manufacturing steps, including cell selection, genetic modification, closed-system manufacturing, and product storage. This comprehensive approach enhances Singapore's ability to develop and produce high-quality cell therapies locally, which is crucial for reducing treatment time and improving patient outcomes.

A*STAR's Role in Advancing CGT

(https://research.a-star.edu.sg/articles/features/editing-the-basics/)

A*STAR has recognized the potential of CGT and continues to play a pivotal role in advancing CGT research in Singapore. A*STAR's institutes, including the Institute of Molecular and Cell Biology (IMCB), the Genome Institute of Singapore (GIS), and the Bioprocessing Technology Institute (BTI) - are at the forefront of CGT innovation, focusing on gene editing technologies, messenger RNA (mRNA) therapies and lipid nanoparticles for efficient delivery to target tissues. They are also developing artificial intelligence (AI) for foundational RNA modeling and therapeutic design in partnership with other A*STAR Institutes like Institute of High Performance Computing (IHPC) and Institute for Infocomm Research (I2R). Additionally, A*STAR's Bioprocessing Technology Institute (BTI) supports scale-up and integration of unit operations up to 50 litres in pre-cGMP settings, facilitating the development of innovative bioprocesses for cell and gene therapies.

Singapore CGT Ecosystem Collaborations

(https://research.a-star.edu.sg/articles/features/editing-the-basics/)

- Nucleic Acid Therapeutics Initiative (NATi): Hosted by A*STAR, this initiative aims to establish Singapore as a hub for NAT research and commercialization. The NATi mRNA BioFoundry was launched to scale up mRNA production during health emergencies.
- Singapore Cell Therapy Advanced Manufacturing Programme (STAMP): Initiated in 2019, STAMP 1.0 brought together public research agencies and biotech industry players to improve cell therapy manufacturing. STAMP 2.0 focuses on developing new manufacturing technologies for cell therapies.
- Process Accelerator for Cell Therapy Manufacturing (PACTMAN): A collaboration between A*STAR and ACTRIS, this joint lab optimizes cell therapy assets and production processes.
- iPSCs-differentiated Natural Killer cells for cancer immunotherapies (PANAKEIA): Combining efforts from A*STAR, SingHealth, and the National University of Singapore, PANAKEIA is developing a platform for producing iPSC-based NK cells for cancer treatments.

EDDIE TAN
DUKE-NUS MEDICAL SCHOOL

Private Sector Investments in Manufacturing Infrastructure

Beyond government initiatives, private companies have also established significant CGT manufacturing capabilities in Singapore. In July 2023, SCG Cell Therapy opened a first-of-its-kind cell therapy GMP-certified facility and research and development center at its headquarters in Singapore, with support from the Singapore Economic Development Board (https://www.pharmaceutical-technology.com/projects/scg-manufacturing-facility-singapore/). Singapore was selected for this facility due to its world-class research and manufacturing infrastructure, pool of GMP-certified manufacturing talent, and business environment receptive to new technologies.

Another notable development is the collaboration between BetaLife and A*STAR to develop next-generation cell-based therapy for diabetes treatment. BetaLife, a stem cell therapy company focused on regenerative medicine for diabetes, has acquired rights to human induced Pluripotent Stem Cell (iPSC) technology and cell lines from A*STAR.

This technology enables the generation of iPSCs, providing a renewable resource to generate mature cell types. BetaLife and A*STAR are also embarking on a research collaboration to generate human iPSC banks that capture the genetic diversity of Asian ethnicities and develop human iPSC-derived pancreatic islet cells. This partnership aims to pave the way for potential cell replacement therapy for diabetes. (https://www.betalife.sg/betalife-and-astar-collaborate-to-develop-next-generation-cell-based-therapy-for-diabetes-treatment-2/)

Breakthrough Clinical Trials and Treatments

Asia's First Multi-Centre Gene Therapy Trial for Heart Failure

In November 2024, the Cardiovascular Disease National Collaborative Enterprise (CADENCE) and Medera Inc.'s Sardocor initiated a ground-breaking clinical trial for a novel gene therapy product aimed at treating heart failure (https://www.cris.sg/cadence-and-medera-launch-asia-s-first-multi-centre-gene-therapy-trial-for-heart-failure/, https://www.biospectrumasia.com/news/98/25257/cadence-and-medera-launch-asias-first-multi-centre-gene-therapy-trial-in-singapore-for-heart-failure.html).

This marks the first multi-centre gene therapy trial in Asia for heart failure, with Singapore being the first and only site selected outside of the United States.

The gene therapy product, SRD-001, employs an adeno-associated virus-based therapy delivered directly to cardiac ventricular muscle cells via Sardocor's proprietary intracoronary infusion system. This therapy is specifically intended to treat patients with heart failure with reduced ejection fraction (HFrEF), which accounts for half of all heart failure cases worldwide (https://www.biospectrumasia.com/news/98/25257/cadence-and-medera-launch-asias-first-multi-centre-gene-therapy-trial-in-singapore-for-heart-failure.html). The trial represents a significant milestone in cardiovascular cell and gene therapy research in Asia and highlights Singapore's position as a leader in this field.

Novel T Cell Therapies for Cancer Treatment

Singapore has made remarkable progress in developing innovative T cell therapies for cancer treatment.

In 2023, a new type of chimeric antigen receptor (CAR) T-cell therapy developed by home-grown biotechnology company CytoMed Therapeutics began clinical trials at the National University Cancer Institute, Singapore (NCIS) (https://www.nuhs.edu.sg/research/research-stories/novel-car-t-cell-therapy-developed-in-singapore-begins-trial-at-the-national-university-cancer-institute-singapore-ncis).

This therapy uses a subtype of immune cells that can be modified from healthy donors and reinfused into unrelated patients without the need for matching.

Additionally, a team of doctors in Singapore has developed a new CAR-T cell therapy for patients with T-cell acute lymphoblastic leukaemia (T-ALL) who have exhausted all other forms of treatment8. This experimental treatment has shown promising results, with 16 patients achieving complete remission within a month of treatment, despite previously having less than a 10% chance of survival (https://www.channelnewsasia.com/singapore/cancer-experimental-treatment-singapore-doctors-t-cell-acute-lymphoblastic-leukaemia-4659386).

SCG Cell Therapy Pte Ltd from Singapore has received clearance from Health Sciences Authority for clinical trials of SCG101, a T-cell therapy targeting hepatitis B-related liver cancer. SCG101, which recognizes the hepatitis B virus surface antigen, aims to eliminate cancer cells and HBV covalently closed circular DNA. It is the first TCR-T cell therapy approved by China's National Medical Products Administration for this cancer, marking the first multi-regional IND approval in cell therapy between Singapore and China. (https://www.biospectrumasia.com/news/26/20248/singapore-approves-clinical-trial-of-tcr-t-cell-therapy-for-liver-cancer.html)

Challenges and Future Prospects

Cost and Accessibility Concerns

Despite the promising advancements in CGT, cost remains a significant challenge. For example, Kymriah Chimeric Antigen Receptor T-cell therapy reportedly costs approximately US$475,000 (S$637,000) (https://www.straitstimes.com/singapore/health/new-manufacturing-facility-task-force-set-up-as-s-pore-ups-game-in-cell-and-gene-therapy).

However, subsidies are available for certain CTGTPs like Kymriah, as listed by MOH, and the increasing local manufacturing capabilities, such as the ACTRIS facility, could potentially help reduce costs in the future.

Currently, Singapore sees about 100 patients each year who require cell and gene therapy treatments, typically offered to those who have not responded well to conventional treatments for conditions such as aggressive leukaemia and lymphoma (https://www.straitstimes.com/singapore/health/new-manufacturing-facility-task-force-set-up-as-s-pore-ups-game-in-cell-and-gene-therapy). As these therapies become more established and manufacturing capabilities expand, their accessibility may improve.

Upcoming Industry Events and Knowledge Exchange

Singapore continues to position itself as a hub for CGT knowledge exchange and networking. Singapore will host the 16th Annual Meeting of the Asian Cellular Therapy Organization (ACTO) from August 14-16, 2025. Additionally, the ISCT Asia Regional Meeting will be held in Singapore from September 2-5, 2026. These gatherings will unite industry leaders to discuss innovations in cell and gene therapy across Asia, share best practices in manufacturing and process development, explore scale-out strategies, optimize costs, and review regulatory case studies. Attendees will have the opportunity to witness the latest scientific advancements, clinical studies, and success stories in this domain. These events serve as essential platforms for stakeholders to exchange ideas, build partnerships, and advance the field.

Conclusion

Singapore has established itself as a significant player in the cell and gene therapy landscape in Asia through strategic investments in infrastructure, regulatory frameworks, and clinical research. The opening of the ACTRIS facility, breakthrough clinical trials, and the implementation of a fit-for-purpose regulatory framework have positioned Singapore as a hub for CGT innovation and development.

While challenges such as cost and accessibility remain, the continued focus on manufacturing capabilities, research and development, public-private partnerships, and government subsidies for clinically- and cost-effective CTGTPs suggests a promising future for cell and gene therapies in Singapore. As the field evolves, Singapore's comprehensive ecosystem approach, combining research excellence, manufacturing capabilities, regulatory oversight, and clinical expertise, will likely continue to drive advancements in this transformative area of medicine.

Professor Emeritus, Chen-Kung Chou, PhD

Department of Life Sciences and Institute of Genome Sciences
National Yang Ming Chiao Tung University, Taipei, Taiwan

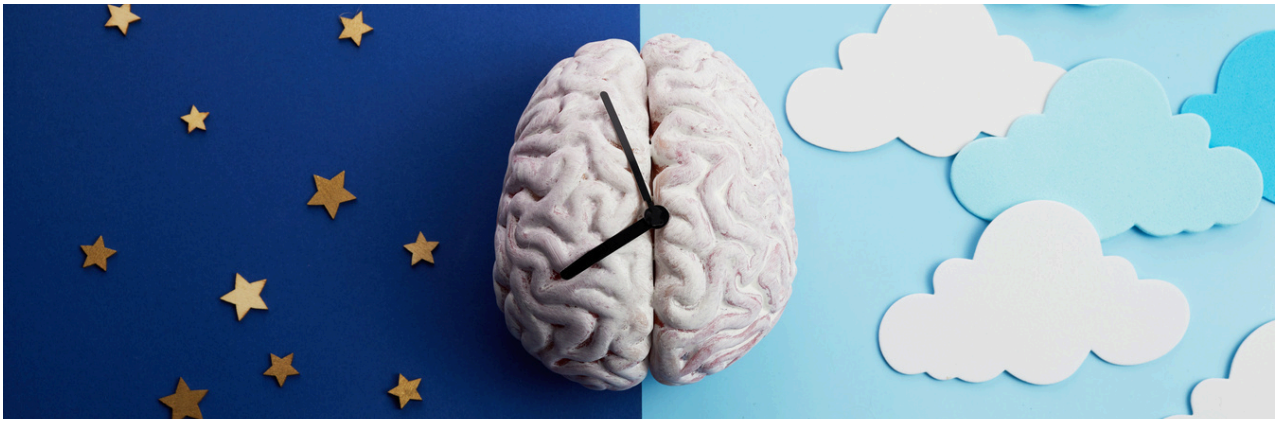


IMAGE FROM CANVA.COM

The Symphony of Time: How Circadian Rhythms Shape Life and Medicine

From the first flicker of life on Earth, the cycle of day and night has been an inescapable backdrop—steady, rhythmic, and profoundly influential. As life evolved, it began not only to respond to this 24-hour cycle but to anticipate it. Today, we know this predictive biological timing system as the circadian rhythm, an internal clock that ticks within virtually every organism—from cyanobacteria to humans.

A Plant in the Dark

The story of circadian rhythms begins not with a microscope, but with a humble plant. In 1729, French astronomer Jean Jacques d'Ortous de Mairan placed a sensitive mimosa in total darkness. To his surprise, the plant's leaves still opened during the day and closed at night. This suggested that an internal mechanism—rather than sunlight—was dictating its behavior. This pioneering experiment marked the birth of circadian biology.

Centuries later, in 1959, American physiologist Franz Halberg coined the term "circadian," from the Latin circa diem(about a day), to describe these near-24-hour cycles in physiology. But what exactly orchestrates these rhythms deep within our cells? That mystery remained unsolved until the 1970s.

The Drosophila Clockmaker

The key to unlocking circadian biology came from an unlikely place: the behavior of fruit flies. Physicist-turned-biologist Seymour Benzer and his graduate student Ronald Konopka at Caltech devised a strategy to mutate and screen fruit flies for abnormalities in their emergence timing—when they hatched from their pupal cases.

After analyzing nearly 2,000 flies, they identified three groundbreaking mutations in a single gene, which they aptly named period (per). One mutation caused no rhythmicity (per^0), another shortened the cycle to 19 hours (per^s), and a third lengthened it to 28 hours (per^l). These findings, published in 1971, showed for the first time that a single gene could govern biological timing. This foundational discovery opened the door to decades of circadian research.

The Gene That Sang

Enter Jeffrey Hall, Michael Rosbash, and Michael Young—three scientists whose paths converged to identify and clone the per gene. Their race culminated in 1984, when all three labs successfully isolated the gene, paving the way for molecular dissection of the biological clock. In 2017, they shared the Nobel Prize in Physiology or Medicine for their contributions.

But the story took an even more lyrical turn. In the lab of Hall and Rosbash, postdoc Bambos Kyriacou discovered that fruit fly mating songs—wing-generated courtship pulses—also followed rhythmic cycles. And when the team examined these songs in per mutants, they found the rhythm of the love song matched the circadian mutations: shorter rhythms sang faster songs, longer rhythms sang slower ones. It became clear that per didn't control just one biological metronome—it was a master conductor of multiple internal clocks.

From Brain to Body: A Whole Symphony of Clocks

We once thought the brain's suprachiasmatic nucleus (SCN) was the sole timekeeper. But in the early 2000s, researchers discovered a symphony of clocks scattered throughout the body—in the liver, skin, heart, lungs, kidneys, and even immune cells. Each peripheral clock maintains its rhythm but takes cues from the SCN, harmonizing like instruments under a conductor's baton.

However, when these rhythms fall out of sync—a condition known as circadian misalignment—disruption ensues. Jet lag is a familiar example, but so is the metabolic confusion triggered by midnight snacks. The liver, expecting rest, poorly handles glucose, while insulin signals collide with a brain set to sleep. Over time, this discordance can lead to chronic disease.

The Rise of Chronomedicine

These insights gave birth to chronomedicine—the science of timing treatment to the body's internal rhythms. In the late 1990s, French oncologist Francis Lévi conducted landmark trials showing that chemotherapy administered at optimal times (e.g., 10 p.m.) could nearly double effectiveness and reduce toxicity in colorectal cancer patients. A 2006 trial further showed that male patients benefited significantly from timed therapy, though results in females were more complex—highlighting sex-based differences in circadian pharmacodynamics.

Even cancer cells, it turns out, have clocks. In a vivid experiment, neuro-oncologist Joshua Rubin engineered glioblastoma cells to glow rhythmically using a fluorescent circadian gene. The cells "blinked" with life, and intriguingly, they responded best to the chemotherapy drug temozolomide when the circadian gene Bmal1 peaked in expression. If we could one day determine a patient's tumor rhythm, we might tailor treatments for maximal efficacy.

Timing Is Everything—even in Surgery

Chronomedicine extends beyond cancer. In a 2018 study, patients undergoing cardiac surgery in the afternoon had half the complication rate compared to morning patients. Researchers linked this to another clock gene, Rev-Erbα, which peaks in the morning and may leave the heart more vulnerable to stress. Blocking Rev-Erbα in mice reduced post-surgical damage—a tantalizing lead for human applications.

And in pharmacology? Nearly half of the top 100 best-selling drugs in the U.S. target genes with circadian expression. Many, like cholesterol-lowering statins with short half-lives, work best when taken at night—when the liver's cholesterol production surges. Yet most prescriptions ignore timing altogether.

The Ancient Clock: A Chinese Perspective

Interestingly, the concept of aligning treatment with time is not new. Over 2,000 years ago, Traditional Chinese Medicine proposed the "Twelve Meridian Clock," in which each two-hour block of the day corresponds to heightened activity in a particular organ. The idea that physiological processes vary predictably over time is remarkably aligned with modern circadian science.

Conclusion: Time as Therapy

We now stand at the dawn of a new era, where time itself becomes a tool in diagnosis and treatment. As we unravel the molecular cogs of our internal clocks, we move closer to personalized medicine that doesn't just ask "what" to prescribe—but also when.

Like a symphony, our body's rhythms require precise coordination. Disrupt the tempo, and the music falters. Respect the rhythm, and we may find a new harmony in healing.

References

1. The Little Flies and their Genes: Nobel Lecture, December 8, 2017 by Jeffrey C. Hall.
2. Time Trails. Nature 556: 290-292; 2018

Professor Chou is a distinguished academic with a rich educational and professional background in the life sciences. He completed his B.S. in Chemistry at Chung-Yung Christian College from 1967 to 1971 and earned his Ph.D. in Molecular Biology from the Albert Einstein College of Medicine between 1974 and 1979. His professional journey began as an Associate Fellow at the Institute of Biological Chemistry, Academia Sinica, Taiwan, from 1979 to 1981.

He then served at the Taipei Veterans General Hospital in the Department of Medical Research, progressing from Associate Investigator to Investigator from 1981 to 2001.

Professor Chou held a professorship at Yang Ming University in the Department of Life Science and served as Chairman of the Institute of Genetics before joining Chang Gung University in 2004, where he currently serves as a Professor in the Department of Life Sciences. His research interests focus on the growth control of human hepatoma cells and the anti-HBV and anti-aging properties of Chinese herbal medicines. Throughout his career, Professor Chou has been recognized with numerous honors, including the Distinguished Scientist award and multiple Outstanding Research Awards from the National Science Council, as well as a Fogarty International Fellowship.

Tony Yu-Xiu Lin, Thai-Yen Ling
Department and Graduate Institute of Pharmacology, National Taiwan University, College of Medicine, Taipei, Taiwan

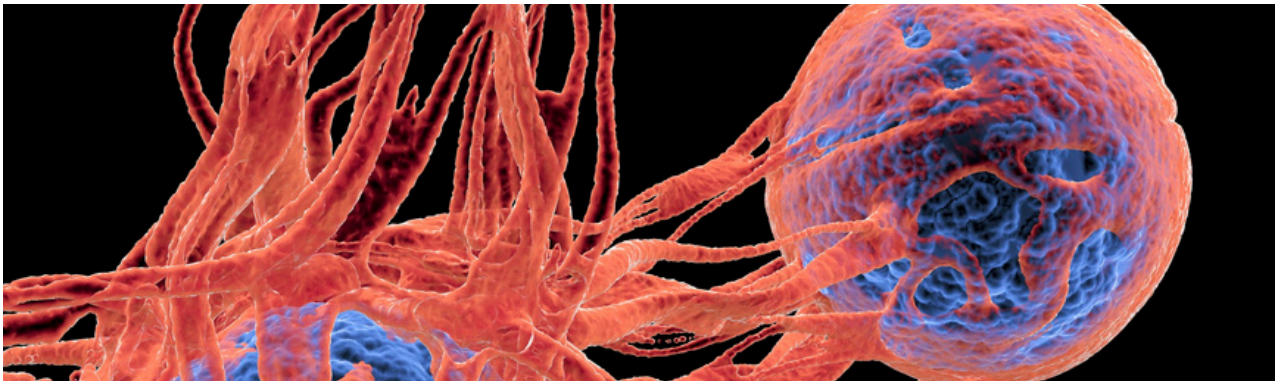


IMAGE FROM CANVA.COM

From Circadian Rhythm to Primary Ovarian Insufficiency: A Stem Cell-Based Therapeutic Perspective

Introduction

From the earliest stages of life on Earth, organisms have adapted to the predictable cycles of day and night. This evolutionary adaptation has given rise to the circadian rhythm, an intrinsic 24-hour biological cycle regulating physiological activities across living organisms—from cyanobacteria to humans. Initially studied primarily in the context of sleep, circadian rhythms are now understood to play vital roles in regulating metabolism, immune function, cardiovascular health, and reproductive physiology [1, 2].

Disruption of circadian rhythms has been linked to a range of diseases, including metabolic disorders, cancer, cardiovascular events, and notably, female reproductive failure such as primary ovarian insufficiency (POI) [3]. Recent findings further highlight a bidirectional interaction between ovarian function and systemic circadian regulation —clock genes such as Bmal1, Per2, and Rev-erbα exhibit rhythmic expression in ovarian tissue and are tightly coupled with hypothalamic rhythmic signals. Disruption of this interplay is now thought to contribute to ovulatory dysfunction and fertility decline, paving the way for novel therapeutic strategies, including estrogen-sensitive mesenchymal stem cell (MSC) therapy.

Circadian Rhythm: A Body-Wide Timekeeper

Circadian rhythms are governed by a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which synchronizes peripheral clocks found in virtually all tissues, including the liver, kidneys, heart, lungs, and ovaries.

These peripheral clocks respond not only to cues from the SCN but also to external stimuli like feeding, exercise, and light exposure, maintaining systemic homeostasis [4].

The significance of circadian rhythms in medicine is underscored by studies showing that the timing of drug administration—known as chronotherapy—can significantly alter therapeutic outcomes. For instance, chemotherapy aligned with a patient's circadian rhythm has demonstrated improved efficacy and reduced toxicity compared to conventional dosing regimens [5].

Disruption of Circadian Rhythms in POI

Primary ovarian insufficiency (POI), affecting approximately 1% of women under age 40, is characterized by the early loss of ovarian follicular function, leading to infertility, amenorrhea, hypoestrogenism, and elevated FSH levels. Chemotherapy is a leading cause of iatrogenic POI, as alkylating agents like cyclophosphamide (CTX) induce DNA damage and apoptosis in granulosa and oocyte cells [6].

Recent evidence reveals that ovarian tissues possess their own peripheral circadian clocks, expressing genes such as Bmal1, Per2, Rev-erbα, and Rora, which exhibit rhythmicity and are modulated by both gonadotropins and estrogen. This bidirectional communication between the SCN and ovaries means that circadian rhythm disruption can exacerbate ovarian dysfunction, and vice versa [7]. For example, Bmal1 knockout mice exhibit implantation failure and infertility, while Per2 deficiency affects estrogen receptor stability. Estrogen itself regulates clock genes through estrogen response elements (EREs) [8], while clock proteins like BMAL1/CLOCK influence the transcription of ERα, forming a tightly regulated feedback loop [9].

MSC Therapy as a Strategy to Restore Ovarian and Circadian Function

Conventional hormone replacement therapy (HRT) for primary ovarian insufficiency (POI) can relieve symptoms, but it often fails to restore fertility and carries long-term risks, including an increased likelihood of hormone-sensitive cancers. In contrast, mesenchymal stem cells (MSCs) have gained attention as a regenerative therapy, thanks to their ability to modulate inflammation, promote blood vessel growth, and support damaged tissue microenvironments.

A groundbreaking study by Le et al. (2024) [9] explored this approach using estrogen receptor-positive placenta-derived MSCs (ER⁺pcMSCs). By harnessing the secretome of these cells—including both unprimed conditioned medium (CM) and estradiol-primed CM (E2-CM)—the researchers tested their effects in a cyclophosphamide-induced POI mouse model.

The results were striking. Treatment with CM and E2-CM improved ovarian follicle development and enhanced steroid hormone synthesis, as evidenced by increased expression of enzymes such as CYP19A1 and StAR. Hormonal balance was partially restored, with elevated estradiol (E2), reduced follicle-stimulating hormone (FSH), and increased anti-Müllerian hormone (AMH) levels. At the cellular level, granulosa cell apoptosis was reduced, and angiogenesis was promoted, with angiogenin identified as a critical factor. Most notably, E2-CM treatment reinstated the rhythmic expression of ovarian clock genes—including Per2, Rev-erbα, and Rora—and restored the mice's disrupted behavioral circadian activity. Further analysis revealed that the exosomal microRNAs contained within the MSC secretome were targeting genes implicated in cell death, fibrosis, and circadian regulation, suggesting a broad and coordinated mechanism of action.

This study is the first to show that stem cell therapy—specifically through the use of an estrogen-sensitive MSC secretome—can simultaneously restore both ovarian function and circadian rhythm, marking a significant advance in the treatment of POI.

The interplay between circadian rhythm and ovarian health offers a compelling new paradigm in reproductive medicine. Disruption of the ovarian circadian clock contributes to follicular atresia and infertility, particularly in chemotherapy-induced POI. Yet, targeting this disruption via the secretome of ER⁺ MSCs presents a novel dual-action therapy: one that regenerates ovarian tissue and recalibrates systemic rhythmicity.

References

1. Begemann, K., Rawashdeh, O., Olejniczak, I., Pilorz, V., de Assis, L. V. M., Osorio-Mendoza, J., & Oster, H. (2025). Endocrine regulation of circadian rhythms. npj Biological Timing and Sleep, 2(1), 10.
2. Ono, M., Ando, H., Daikoku, T., Fujiwara, T., Mieda, M., Mizumoto, Y., ... & Fujiwara, H. (2023). The circadian clock, nutritional signals and reproduction: a close relationship. International journal of molecular sciences, 24(2), 1545.
3. Federici, S., Rossetti, R., Moleri, S., Munari, E. V., Frixou, M., Bonomi, M., & Persani, L. (2024). Primary ovarian insufficiency: update on clinical and genetic findings. Frontiers in Endocrinology, 15, 1464803.
4. Shanmugam, D. A. S., Balaraman, A. D., Kar, A., Franco, A., Balaji, B. A. C., Meenakumari, S., ... & Shanthi, B. (2025). Mini review: Bidirectional Regulation of Circadian Rhythm by Suprachiasmatic Nucleus and Nuclear Receptors in Female Mammals. Journal of Circadian Rhythms, 23, 4.
5. Zhou, J., Wang, J., Zhang, X., & Tang, Q. (2021). New insights into cancer chronotherapies. Frontiers in Pharmacology, 12, 741295.
6. Huang, Y., Liu, Z., Geng, Y., Li, F., Hu, R., Song, Y., ... & Song, K. (2025). The risk factors, pathogenesis and treatment of premature ovarian insufficiency. Journal of Ovarian Research, 18(1), 134.
7. iang, Z., Zou, K., Liu, X., Gu, H., Meng, Y., Lin, J., ... & Ding, G. (2021). Aging attenuates the ovarian circadian rhythm. Journal of Assisted Reproduction and Genetics, 38(1), 33-40.
8. Ratajczak, C. K., Boehle, K. L., & Muglia, L. J. (2009). Impaired steroidogenesis and implantation failure in Bmal1−/− mice. Endocrinology, 150(4), 1879-1885.
9. Nakamura, T. J., Sellix, M. T., Menaker, M., & Block, G. D. (2008). Estrogen directly modulates circadian rhythms of PER2 expression in the uterus. American Journal of Physiology-Endocrinology and Metabolism, 295(5), E1025-E1031.
10. Le, D.-C., Ngo, M.-H. T., Kuo, Y.-C., et al. (2024). Secretome from estrogen-responding human placenta-derived mesenchymal stem cells rescues ovarian function and circadian rhythm in mice with cyclophosphamide-induced primary ovarian insufficiency. Journal of Biomedical Science, 31(95).
11. Hogenesch, J. et al. (2014). A time-resolved transcriptome atlas of the mouse. Nature Biotechnology.
12. Lévi, F. et al. (1997 & 2006). Chronotherapy trials in colorectal cancer. Lancet Oncology.

Pham, T. T. Q., YH Huang
Taipei Medical University, Taipei

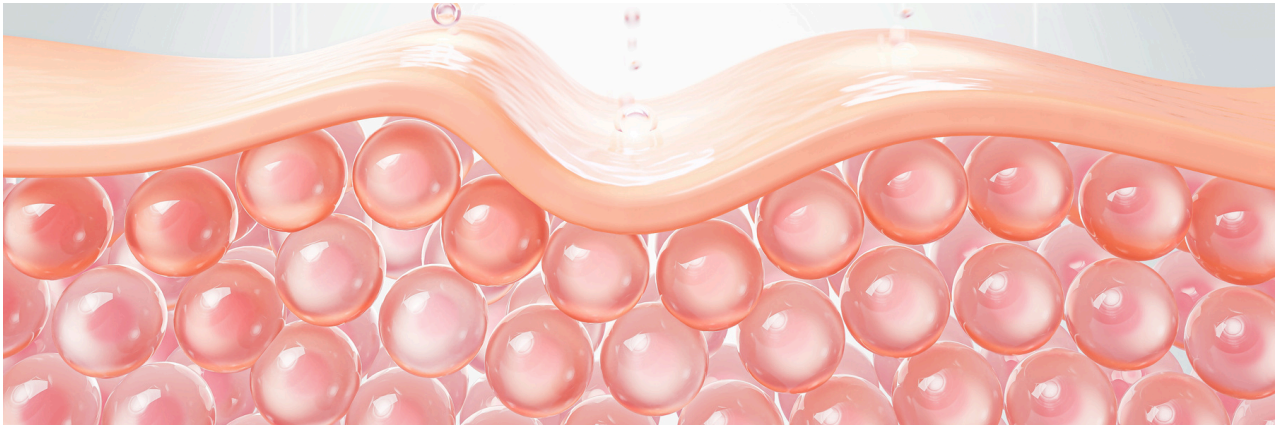


IMAGE FROM CANVA.COM

The Double-Edged Niche: Regulatory Mechanisms in Skin Stem Cells and Cancer

Human skin represents one of nature's most sophisticated examples of tissue homeostasis, functioning as an intricate biological system that seamlessly balances protection, regeneration, and adaptive responses to environmental stressors. Normal skin homeostasis operates through a carefully orchestrated cellular hierarchy, where skin stem cells (SSCs) serve as the foundational architects of epidermal integrity. The outermost layer of our skin, the epidermis, functions not merely as a passive protective barrier but as a dynamic, mechanically responsive tissue that continuously renews itself through precisely regulated cellular processes.

SSCs, a population of long-lived basal stem cells, strategically positioned at the boundary between the epidermis and dermis. These cellular guardians possess the extraordinary capacity for unlimited self-renewal while simultaneously generating daughter cells destined for differentiation. The progeny of these stem cells, known as transient amplifying cells, embark on cellular maturation, progressively moving through distinct epidermal layers as they undergo terminal differentiation, ultimately forming the protective cornified envelope that shields us from environmental harm.

The delicate equilibrium maintained by this cellular ecosystem is fundamental to skin health and function. When this balance is disrupted, the consequences can be catastrophic, leading to hyperproliferative disorders, chronic inflammatory conditions, or the development of malignant neoplasms.

Understanding the mechanisms that govern this balance has become increasingly critical as we witness a global surge in skin cancer incidence, making cutaneous malignancies one of the most pressing public health challenges of our time.

The Escalating Global Burden of Cutaneous Malignancies

The contemporary landscape of skin cancer epidemiology presents a sobering reality that demands urgent attention from the global medical community. Cutaneous malignancies, encompassing both melanoma and non-melanoma variants, have experienced unprecedented increases in incidence rates across diverse populations worldwide.

Melanoma, while representing a smaller fraction of total skin cancer cases, commands particular attention due to its exceptional lethality and aggressive biological behavior. This malignancy demonstrates an almost unparalleled capacity for metastatic dissemination, often occurring through complex mechanisms. According to GLOBOCAN 2022 data, melanoma ranks as the 22nd leading cause of cancer deaths worldwide[1]—underscoring its severe impact. The clinical reality of advanced melanoma presents formidable challenges for both patients and healthcare providers. Individuals diagnosed with stage IV disease face particularly grim prospects, with five-year survival rates hovering around 22.5%[2], despite advances in therapeutic approaches.

This poor prognosis reflects the inherent biological aggressiveness of advanced melanoma, characterized by its remarkable capacity for treatment resistance and genetic instability. Epidemiological modeling suggests that by 2040, global melanoma cases will increase by approximately 50%, with new diagnoses potentially reaching 510,000 annually[3]. Even more alarming is the projected 68% increase in mortality, with deaths potentially rising to 96,000 annually compared to 2020 baseline figures[3].

Melanoma often steals the spotlight because of its deadly nature, but the quieter epidemic of non-melanoma skin cancers affects far more people each year. These mainly include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), both of which pose a significant challenge to healthcare systems worldwide. BCC accounts for about 70% of non-melanoma cases, while SCC makes up around 25%[4]. The epidemiological trends for non-melanoma skin cancers reveal a disturbing pattern of consistent increase over the past three decades. BCC incidence has surged by 20% to 80% annually, while SCC rates have increased by 3% to 10% per year[5]. The year 2022 witnessed 1,234,533 new non-melanoma skin cancer cases globally, resulting in 69,416 deaths according to comprehensive global cancer statistics[6].

SCC, in particular, presents unique challenges due to its aggressive biological behavior and capacity for invasive growth. This malignancy contributed to approximately 56,000 deaths in 2019 according to global health surveys, highlighting its significant mortality impact[7]. When SCC progresses to invasive stages, the prognosis becomes particularly dire, with 10-year survival rates dropping below 20% for advanced cases[8]. The global burden of cutaneous SCC reached 2,402,221 cases in 2019, with death rates increasing by 6.1% between 1990 and 2019[9]. Projections for 2035 estimate 3,637,626 cases, representing a staggering 51.4% increase from 2019 levels[9].

Skin cancer stem cells: the architects of treatment resistance

The concept of skin cancer stem cells (CSCs) has revolutionized our understanding of malignant biology, particularly in the context of cutaneous malignancies. These specialized cellular populations possess characteristics that set them apart from bulk tumor cells, including enhanced self-renewal capacity, resistance to conventional therapeutic approaches, and the ability to generate heterogeneous tumor populations. In aggressive skin cancers, the persistent self-renewal and expansion of CSCs correlate directly with poor clinical outcomes, treatment resistance, and invasive behavior.

The identification and characterization of CSC populations in skin malignancies have revealed remarkable cellular diversity and complexity. In melanoma, researchers have identified multiple distinct CSC subpopulations, each characterized by specific molecular markers and functional properties. These include cells expressing CD133 (Cluster of Differentiation 133), a glycoprotein associated with stem cell properties and treatment resistance[10]. Additionally, ABCB5-positive cells, characterized by expression of ATP-binding cassette sub-family B member 5, demonstrate enhanced drug efflux capabilities that contribute to chemotherapy resistance[11].

The enzyme aldehyde dehydrogenase (ALDH) serves as another critical marker for melanoma CSCs, playing essential roles in cellular metabolism and detoxification processes that enhance survival under therapeutic stress[12]. CD20-positive melanoma cells represent yet another distinct subpopulation with stem cell characteristics[13], while CD271-expressing cells demonstrate particular relevance to neural crest-derived melanoma biology[14]. The transcription factor SOX10 (SRY-Box transcription factor) marks additional CSC populations that maintain developmental programs associated with melanocyte lineage specification[15].

Similarly, SCC and BCC harbor distinct cancer stem cell subpopulations that contribute to tumor initiation, progression, and therapeutic resistance. These cellular populations demonstrate remarkable plasticity, adapting to therapeutic pressures through various mechanisms including metabolic reprogramming, enhanced DNA repair capabilities, and activation of survival signaling pathways.

The microenvironmental niche: orchestrating cellular fate decisions

The fate determination of both normal SSCs and CSCs occurs within specialized microenvironmental niches that provide essential regulatory signals and structural support. These niches function as sophisticated cellular ecosystems where multiple cell types, signaling molecules, and structural components collaborate to maintain tissue homeostasis or, alternatively, promote malignant transformation and progression.

In normal SSC niches, several core signaling pathways maintain the delicate balance between self-renewal and differentiation. The Sonic Hedgehog (Shh) pathway plays fundamental roles in stem cell maintenance and tissue patterning, regulating cellular proliferation and differentiation decisions through complex transcriptional networks.

The Wingless-related integration site (Wnt)/β-catenin signaling cascade serves as another critical regulatory mechanism, controlling stem cell fate decisions and tissue regeneration processes. The Notch signaling pathway contributes additional layers of regulation, mediating cell-cell communication and fate specification through direct intercellular interactions. Meanwhile, the YAP (Yes-associated protein)/TAZ (Transcriptional co-activator with PDZ-binding motif) pathway integrates mechanical and biochemical signals to regulate stem cell behavior and growth. These pathways work together with other parts of the stem cell niche—such as adhesion signals, the dermal-epidermal border, and the surrounding diverse cells—to keep stem cells in balance. It's a fine-tuned act: providing just enough activity to preserve their regenerative potential while preventing uncontrolled growth. This quiet coordination draws the line between healthy tissue renewal and unchecked proliferation.

However, in CSC niches, this carefully orchestrated regulatory system becomes dysregulated, leading to aberrant cellular behavior and malignant transformation. In treatment-resistant skin cancers, CSC niches are shaped by a mix of disrupted signals and oncogenic pathways—especially PI3K/AKT/mTOR and JAK/STAT3. These signaling changes don't just help CSCs survive; they actively support their growth and protect them from therapy. Even when treatments manage to target the bulk of the tumor, these niche-driven pathways can help a small group of stem-like cells escape, adapt, and eventually cause the cancer to return. This makes the niche itself a major obstacle, reinforcing resistance and making it harder to fully eliminate the disease. Therefore, understanding and targeting these pathways may be essential to improving outcomes.

Therapeutic implications and future directions

CSCs and their niche are no longer passive footnotes in tumor biology—they are the tacticians behind resistance, relapse, and relentless progression. In many advanced cases, patients face poor outcomes—not just because of the cancer's spread, but because conventional therapies often can't eliminate the small, resilient population of CSCs hiding within complex microenvironments. These cells are experts at survival, protected by signals from their niche. While this insight opens new possibilities for targeted treatments, developing therapies that can effectively disrupt these interactions without harming healthy tissue remains a major challenge. Targeting CSC niches represents a promising therapeutic strategy, particularly for refractory skin cancers that have failed conventional treatment approaches.

This approach recognizes that effective cancer treatment requires not only elimination of bulk tumor cells but also disruption of the specialized microenvironments that sustain CSC populations. Current clinical investigations are exploring various strategies to target niche signaling pathways, including inhibitors of Shh, Wnt, Notch, and YAP/TAZ signaling, as well as combination approaches that simultaneously target multiple pathways.

Key components of the stem cell niche, such as integrins and their ligand laminins, function with a dual identity. Under physiological conditions, they orchestrate orderly epidermal differentiation and tissue stability. However, when their expression patterns are altered, these same molecules shift roles—supporting the survival, self-renewal, and expansion of CSCs. This functional duality presents a therapeutic conundrum: targeting these adhesive signals may suppress tumorigenic potential, but risks disrupting essential regenerative processes in normal skin. Additionally, the dermo-epidermal junction, adherens junctions, and various cell types including immune cells and fibroblasts all contribute to niche function and represent potential therapeutic targets.

Conclusion: toward precision medicine in skin cancer treatment

In this review, we reframed the dynamic dialogue between SSCs and their surrounding microenvironments as a central narrative in both skin maintenance and cancer development[16].

Additionally, we summarized clinical trials targeting core signaling in skin CSC niches and highlight how comprehensive understanding of CSC niche biology can inform effective therapeutic strategies to overcome treatment resistance and improve patient outcomes[16].

Despite strides in decoding these cellular communication, many of the molecular cues that dictate how CSCs engage with their niches remain elusive. Notably, pockets of treatment resistance are often traced back to these resilient cell populations that escape conventional therapies. To move the field forward, future investigations should turn a sharper lens on the two-way communication between cutaneous CSCs and their niche habitats. Unraveling these interactions may hold the key to unlocking more durable therapeutic strategies for skin malignancies and overcoming drug resistance at its root. The development of precision medicine approaches that account for the heterogeneity of CSC populations and their niche dependencies will be essential for improving outcomes in patients with aggressive skin malignancies.

References

1. Sung, H. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71, 209-249 (2021).
2. Hamp, A., Anderson, J., Sivesind, T. E., Szeto, M. D. & Hadjinicolaou, A. From the Cochrane library: systemic treatments for metastatic cutaneous melanoma. JMIR Dermatol 4, e30270 (2021).
3. Arnold, M. et al. Global burden of cutaneous melanoma in 2020 and projections to 2040. JAMA Dermatol 158, 495-503 (2022).
4. Leiter, U., Keim, U. & Garbe, C. Epidemiology of skin cancer: update 2019. In Sunlight, Vitamin D and Skin Cancer, 123-139 (2020).
5. Eide, M. J. et al. Identification of patients with nonmelanoma skin cancer using health maintenance organization claims data. Am J Epidemiol 171, 123-128 (2010).
6. Wang, M., Gao, X. & Zhang, L. Recent global patterns in skin cancer incidence, mortality, and prevalence. Chin Med J (Engl) 138, 185-192 (2025).
7. Zhang, W. et al. Global, regional and national incidence, mortality and disability-adjusted life-years of skin cancers and trend analysis from 1990 to 2019: An analysis of the global burden of disease study 2019. Cancer Med 10, 4905-4922 (2021).
8. Hillen, U. et al. Advanced cutaneous squamous cell carcinoma: A retrospective analysis of patient profiles and treatment patterns-Results of a non-interventional study of the DeCOG. Eur J Cancer 96, 34-43 (2018).
9. Guo, A., Liu, X., Li, H., Cheng, W. & Song, Y. The global, regional, national burden of cutaneous squamous cell carcinoma (1990–2019) and predictions to 2035. Eur J Cancer Care 2023, 5484597 (2023).
10. El-Khattouti, A. et al. Identification and analysis of CD133+ melanoma stem-like cells conferring resistance to taxol: An insight into the mechanisms of their resistance and response. Cancer letters 343, 123-133 (2014).
11. Schatton, T. et al. Identification of cells initiating human melanomas. Nature 451, 345-349 (2008).
12. Luo, Y. et al. ALDH1A isozymes are markers of human melanoma stem cells and potential therapeutic targets. Stem Cells 30, 2100-2113 (2012).
13. Pinc, A. et al. Targeting CD20 in melanoma patients at high risk of disease recurrence. Mol Ther 20, 1056-1062 (2012).
14. Civenni, G. et al. Human CD271-positive melanoma stem cells associated with metastasis establish tumor heterogeneity and long-term growth. Cancer Res 71, 3098-3109 (2011).
15. Shakhova, O. et al. Sox10 promotes the formation and maintenance of giant congenital naevi and melanoma. Nat Cell Biol 14, 882-890 (2012).
16. Pham, T. T. Q., Kuo, Y.-C., Chang, W.-L., Weng, H.-J. & Huang, Y.-H. Double-sided niche regulation in skin stem cell and cancer: mechanisms and clinical applications. Mol Cancer 24, 147 (2025).

D Renovaldi, YH Huang
International PhD Program in Medicine, Taipei Medical University

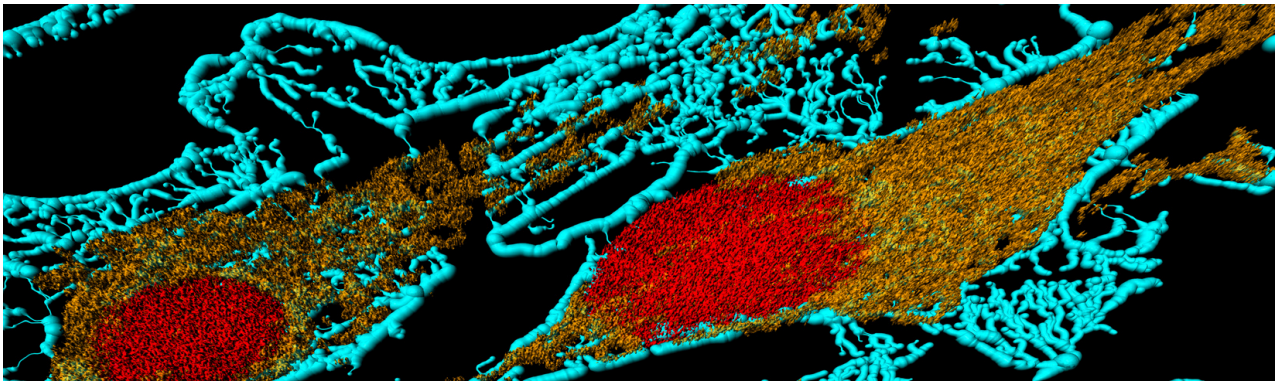


IMAGE FROM CANVA.COM

Harnessing the Tumor Microenvironment: Therapeutic Approaches to Modulate Cancer-Associated Fibroblasts

Introduction

Tumor progression is driven not only by the genetic alterations of cancer cells but also by their interactions with the surrounding tumor microenvironment (TME). The TME comprises various cellular and non-cellular components, including cancer cells, immune cells, blood vessels, extracellular matrix (ECM), and stromal cells, with cancer-associated fibroblasts (CAFs) being one of the most influential types of stromal cells. CAFs are implicated in various processes, including the remodeling of the ECM, secreting cytokines and growth factors, and interacting with other TME cells. Understanding the diverse roles of CAFs and the molecular mechanisms governing their function is essential for developing targeted therapies that could disrupt their tumor-promoting activities and improve the clinical management of cancer (1) (2).

2. Cancer-Associated Fibroblasts: Origin and Characteristics

2.1 Origins and Heterogeneity of CAFs

CAFs originate from various precursor cell types, including tissue-resident fibroblasts, mesenchymal stem cells (MSCs), endothelial cells through endothelial-mesenchymal transition (EndMT), and epithelial cells via epithelial-mesenchymal transition (EMT) (2) (3). Their origin is tissue-dependent and varies across different types of cancer. CAFs are highly heterogeneous, with distinct subpopulations exhibiting varying phenotypic and functional characteristics. Common markers for CAFs include fibroblast activation protein (FAP), alpha-smooth muscle actin (α-SMA), and fibroblast-specific protein-1 (FSP-1), but these markers are not exclusive to CAFs, complicating their identification and functional characterization (3).

The heterogeneity of CAFs arises not only from their diverse origins but also from the dynamic nature of their activation and the signals they receive from the tumor cells and surrounding TME. This diversity allows CAFs to adapt to different tumor stages and environmental conditions, contributing to their multifaceted roles in cancer progression (1).

2.2 Biological Functions of CAFs in Tumor Progression

CAFs play several important roles in promoting tumor progression. One of their key functions is the remodeling of the ECM. Through the secretion of ECM proteins like collagen and fibronectin, CAFs create a supportive scaffold for tumor cells and facilitate cell adhesion, migration, and invasion (3). The altered ECM structure, often denser and stiffer than in normal tissues, can promote tumor cell survival and proliferation, and also hinder immune cell infiltration (2).

CAFs also secrete a variety of growth factors, cytokines, and chemokines, such as TGF-β, VEGF, IL-6, and CXCL12, which modulate tumor cell behavior and the immune response. These secreted factors can support tumor cell growth, induce angiogenesis, and create an immunosuppressive TME, thereby allowing tumors to evade immune surveillance and resist therapy (3).

Furthermore, CAFs interact with immune cells to promote immune evasion. By secreting factors like TGF-β and IL-6, CAFs recruit immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), into the TME, which inhibit the function of tumor-infiltrating lymphocytes (TILs) and prevent effective immune responses (1) (3).

3. Mechanisms of CAF-Mediated Tumor Progression

3.1 CAF mediates ECM Remodeling and Tumor Growth

CAFs are major contributors to the dynamic remodeling of the ECM, which is a crucial process for tumor progression. The ECM not only provides structural support to the tumor but also acts as a regulatory component of cellular behavior. CAFs secrete matrix metalloproteinases (MMPs), which degrade the ECM, facilitating tumor cell migration and invasion(2). CAFs also influence the mechanical properties of the ECM, making it stiffer and more resistant to normal tissue architecture, which can further support the growth and spread of tumor cells (3).

In addition to ECM degradation, CAFs also secrete various cytokines and growth factors that promote the survival and proliferation of tumor cells. These factors, such as epidermal growth factor (EGF) and hepatocyte growth factor (HGF), activate signaling pathways that enhance tumor cell survival and motility (3).

3.2 CAF regulates Immune Modulation

CAFs play a pivotal role in shaping the immune landscape of the TME. By secreting immunosuppressive cytokines such as TGF-β and IL-6, CAFs create an environment that favors immune evasion. These cytokines recruit immunosuppressive cells, such as Tregs and MDSCs, which inhibit the activity of tumor-infiltrating lymphocytes (TILs) (3). This immunosuppressive niche not only allows tumors to escape immune surveillance but also contributes to resistance against immunotherapies.

In addition to their direct effects on immune cells, CAFs also contribute to the creation of a "physical barrier" by remodeling the ECM, which hinders the infiltration of immune cells into the tumor tissue (2). The dense ECM produced by CAFs can physically restrict immune cell movement and prevent them from effectively targeting tumor cells.

3.3 CAF induces Angiogenesis

CAFs are also involved in promoting angiogenesis, the process by which new blood vessels are formed to supply nutrients and oxygen to growing tumors. CAFs secrete pro-angiogenic factors, such as VEGF and PDGF, which stimulate the growth of blood vessels and enhance tumor vascularization (1). This increased blood supply not only supports tumor growth but also facilitates the dissemination of tumor cells to other parts of the body. Additionally, CAFs can alter the properties of blood vessels, making them more permeable and promoting the infiltration of immune cells and other stromal cells (3).

4. Targeting CAFs in Cancer Therapeutics

4.1 CAF Depletion

Depleting CAFs is one of the most direct approaches to disrupt their pro-tumorigenic functions. This can be achieved through various strategies, such as the use of chimeric antigen receptor (CAR)-T cells targeting FAP-expressing CAFs (2). The depletion of CAFs has been shown to reduce tumor growth and increase the effectiveness of immune therapies by alleviating immune suppression in the TME (3).

Additionally, nanoparticle-based drug delivery systems (NDDS) are being developed to target CAFs. These systems can passively target CAFs based on the altered properties of the TME, such as increased permeability in the tumor vasculature(3). By delivering drugs directly to CAFs, NDDS can promote CAF depletion and reduce their ability to support tumor progression.

4.2 CAF Reprogramming and Normalization

Another strategy involves reprogramming CAFs from a pro-tumorigenic to a tumor-suppressive phenotype. This can be achieved through the use of small molecules or gene therapy approaches that block the activation of CAFs or induce their conversion into quiescent fibroblasts (2). For example, inhibiting TGF-β signaling in CAFs has been shown to reduce their tumor-promoting activities and improve the TME (3).

The normalization of CAFs can also be achieved by targeting the pathways that regulate ECM remodeling and immune modulation. By reversing the activated state of CAFs, it is possible to restore a more favorable TME that supports effective immune responses and reduces tumor growth (3).

4.3 CAF Modulation on Tumor Cells and ECM

Nanomedicines are being developed to modulate the effects of CAFs on both tumor cells and the ECM. These therapies aim to inhibit the secretion of cytokines and growth factors by CAFs, thereby reducing tumor cell survival and invasion(3). For example, nanoparticles loaded with drugs that target CAF-derived ECM components can reduce tumor stiffness and improve drug delivery (2).

Additionally, therapies aimed at modulating the physical properties of the ECM, such as reducing its rigidity, can enhance the infiltration of immune cells and improve the efficacy of chemotherapy and immunotherapy (1).

5. Clinical Trials Targeting CAFs and Tumor Microenvironment

Several clinical trials are underway to explore therapies targeting the CAFs and TME, focusing on CAF depletion, reprogramming, and ECM remodeling.

- **FAP-Targeted CAR-T Cells**

Chimeric antigen receptor (CAR)-T cells targeting fibroblast activation protein (FAP) expressed by CAFs have been tested in preclinical studies and are currently being evaluated in clinical trials. One such trial, NCT03099159, focuses on using CAR-T cells to target FAP+ CAFs in solid tumors. The aim is to reduce the supportive stromal elements that enable tumor growth and metastasis.

- **Losartan for ECM Remodeling**

Losartan, a drug that inhibits collagen production by CAFs, has been evaluated in clinical trials as an adjunct to chemotherapy. A phase II trial, NCT01821729, investigated the combination of losartan with chemotherapy in patients with pancreatic cancer to reduce ECM stiffness and improve drug delivery (1).

- **Anti-FAP Antibodies**

A clinical trial (NCT02314296) is testing the use of FAP-targeted monoclonal antibodies in combination with chemotherapy for patients with advanced solid tumors. The goal is to selectively target CAFs and reduce tumor-supporting ECM production, ultimately improving therapeutic outcomes (2).

- **TGF-β Inhibition**

TGF-β is a key regulator of CAF activation and ECM remodeling. Clinical trials targeting TGF-β signaling, such as NCT02925304, aim to inhibit CAF activation in various cancers, to reverse the pro-tumorigenic effects of CAFs, and enhance the effectiveness of other cancer therapies (3).

These trials are promising, but challenges remain in selectively targeting CAFs without affecting normal tissue function. Ongoing research into the heterogeneity of CAFs and better targeting strategies is crucial for improving the clinical success of these therapies (2) (3).

6. Challenges and Future Directions

Despite the promising potential of CAF-targeted therapies, several challenges remain. The heterogeneity of CAFs, with their dual roles as both tumor-promoting and tumor-suppressive cells, complicates the development of universal therapies(2). Furthermore, the dense and abnormal vasculature in the TME presents barriers to effective drug delivery, necessitating the development of advanced delivery systems like nanoparticles (3).

Future research should focus on identifying biomarkers that distinguish between tumor-promoting and tumor-suppressive CAFs and developing strategies to target specific CAF subpopulations. Additionally, combining CAF-targeted therapies with conventional treatments like chemotherapy and immunotherapy may provide more effective cancer treatments (3).

7. Conclusion

CAFs are central to the progression of solid tumors, influencing tumor growth, immune evasion, and treatment resistance. Targeting CAFs through depletion, reprogramming, and modulation represents a promising therapeutic approach to alter the TME and improve cancer treatment outcomes. However, the complexity of CAF biology and the challenges posed by the TME require continued research and innovation to optimize these therapies and achieve better clinical results.

References

1. Yamazaki M, Ishimoto T. Targeting Cancer-Associated Fibroblasts: Eliminate or Reprogram? Cancer Sci. 2025;116(6):613-621. doi:10.1111/cas.16443.
2. Wang Y, Zhou H, Ju S, Dong X, Zheng C. The Solid Tumor Microenvironment and Related Targeting Strategies: A Concise Review. Front Immunol. 2025;16:1563858. doi:10.3389/fimmu.2025.1563858.
3. Zou L, Xian P, Pu Q, Song Y, Ni S, Chen L, Hu K. Nano-Drug Delivery Strategies Affecting Cancer-Associated Fibroblasts to Reduce Tumor Metastasis. Acta Pharm Sin B. 2025;15(4):1841-1868. doi:10.1016/j.apsb.2025.02.040.
4. National Institutes of Health. FAP-Targeted CAR-T Cells in Solid Tumors. Available from: https://clinicaltrials.gov/ct2/show/NCT03099159.
5. National Institutes of Health. Losartan in Combination with Chemotherapy in Pancreatic Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT01821729.
6. National Institutes of Health. Anti-FAP Antibodies in Combination with Chemotherapy for Advanced Solid Tumors. Available from: https://clinicaltrials.gov/ct2/show/NCT02314296.
7. National Institutes of Health. TGF-β Inhibition in Solid Tumors. Available from: https://clinicaltrials.gov/ct2/show/NCT02925304.

Joseph Wangisani Chisaka
Department of Biochemistry and Molecular Cell Biology,
Taipei Medical University, Taipei, Taiwan

IMAGE FROM CANVA.COM

From Lab to Therapy: Unraveling Therapeutic Potentials of Functional Engineered Extracellular Vesicles

Introduction

Extracellular vesicles (EVs) are emerging as powerful tools for targeted therapy of a wide range of pathologies through functional transfer of biomolecular cargoes, such as nucleic acids, lipids and proteins, to recipient cells and regulate their downstream signaling pathways to modulate their fate. As naturally occurring delivery vehicles, EVs possess a number of advantageous characteristics, including unique size and structure, excellent biocompatibility, immunologically inert, increased stability in circulation, intrinsic targeting capacity and the capability of membrane fusion and crossing of biological barriers (Cai et al., 2024)(Lu et al., 2023). According to inquiries in the NCBI PubMed database, there has been an increase of 211% in EVs publication between the 5 years period of 2019–2024 (8,145 publications) compared to the 5 years period between 2014–2019 (3,113 publications), with a relatively higher fraction of the publications investing the transport of small molecules, macromolecular complexes, and nucleic acids.

This reflects a booming research interest and EVs widening application potential in therapeutics and diagnostics (Li et al., 2025).However, despite the great potential for their clinical application, challenges with cargo loading and EVs low yield continue to be reported as significant obstacles for EVs transitioning from experimental research to clinical practice. As such, strategies for enhancing EV cargo-loading and promoting EV release would have broader application prospects with substantial outcomes. This has resulted in recent growing interest in engineering EVs to specifically alter their cargo. Although concerns have been raised regarding the natural body processes which function to eliminate foreign protein or nucleic acid drugs whenever they are introduced into the body by the immune response. However, in the case of the EVs, the vesicle structure acts as a protection cover for the drug molecules against internal immune elimination (Wang et al., 2025).

EVs engineering

The delivery properties of EVs can be improved by genetic engineering of parent cells (endogenous modification) or direct modification of the EVs (exogenous modification). In the endogenous modification, parent cells are altered before EVs are isolated to make the secreted EVs carry specific molecules. For example, a vector containing the target gene can be transfected into parent cells using genetic engineering technology. The parent cells then produce and secrete proteins or ncRNAs encoded by the inserted genes and package them into EVs through a natural packaging process (Lu et al., 2023)(Wang et al., 2025). EVs enriched with target proteins or nucleic acids can therefore be obtained by purifying the cell culture supernatant. This EV biosynthesis system is limited based on the fact that the sorting system utilized by the cells to determine which substances are packaged into EVs is so complex. As a result, this limits specificity and often result in random packaging into EVs and low loading efficiency (Wang et al., 2025).

On the other hand, exogenous modification involves loading target molecules directly onto isolated and purified EVs through different engineering techniques which include co-incubation, electroporation, extrusion, ultrasonic treatment, calcium chloride-mediated transfection, saponin permeabilization, freeze-thaw cycles etc. (Wang et al., 2025).

Recent advances in functional EV engineering

As organic nanoparticles, functional engineered EVs generally exhibit lower toxicity and fewer adverse reactions. However, they often suffer from poor stability and suboptimal biodistribution, requiring many modifications to achieve effective cargo delivery. Below are some of the engineering techniques adopted in recent researches to address some of the EVs engineering challenges earlier discussed:

Microfluidics: A promising technology which enables the use of small devices and minimal sample amounts for exosome collection, loading and detection while providing ease of scalability compared to traditional methods. Researchers have recently employed this technology to facilitate the generation, modification, and loading of exosomes and exosome-mimetic nanovesicles in a highly efficient and precise manner.

Nanopration: Another innovative technology that employs nanofluidic devices with nanochannel electroporation and enables efficient loading of specific cargos into exosomes with high effectiveness. This technology has already shown success in various preclinical models despite being recently developed and has offered relatively similar advantages to those of microfluidic systems.

Genetic engineered sorting: Cargo loading is achieved prior to exosome isolation under this technology, which minimizes loss or damage to exosomes. It preserves the structural integrity of exosomes from exposure to freeze–thaw cycles and destabilizing temperatures as is the case with electroporation techniques. However, due to the genetic engineering constraints, this method is only suitable for cargos naturally produced within cells, thus excluding small molecule drugs (Liu et al., 2025).

Engineered EVs in clinical trials

Advances in EVs engineering have enabled precise therapeutic delivery and investigation in clinical trials. A survey on Clinical Trials.gov (https://clinicaltrials.gov/) shows the major applications of exosomes are biomarkers, exosome-therapy, drug delivery systems, and cancer vaccines. An analysis shows that a total of 116 trials have been recorded of which 6 (5.17%) studies were for drug-delivery system trials (Rezaie, Feghhi and Etemadi, 2022). An on-going phase I trial is investigating the intravenous delivery of siRNA-loaded Bone Marrow MSC-derived exosomes targeting KRAS G12D mutations in metastatic Pancreatic Ductal Adenocarcinoma (PDAC) patients who failed multiple lines of therapy (NCT03608631). Another on-going phase II trial is investigating whether sub-endometrial injection of mechanically engineered umbilical cord-derived stem cell exosomes can improve endometrial thickness or clinical pregnancy rates compared to platelet-rich plasma in severe intrauterine adhesions following adhesiolysis (NCT06896747).

Conclusion

EVs have generated massive interest as a promising therapeutic option on a wide range of diseases with unmet needs through their demonstrated high biocompatibility and low immunogenicity as natural cell products, stability due to the lipid bilayer that protects from enzymatic degradation, and the ability to cross biological barriers which enhance their targeting capabilities. On the other hand, engineered EVs can further provide enhanced precision in targeted disease therapeutics. While EVs may be synthesized in Good Manufacturing Practice (GMP) settings, significant issues related to immunogenicity (especially engineered EVs), safety, toxicity, biodistribution, and targeting persist.

References

- Cai, H. et al. (2024) 'Delivering synaptic protein mRNAs via extracellular vesicles ameliorates cognitive impairment in a mouse model of Alzheimer's disease', BMC Medicine, 22(1), pp. 1–18. doi:10.1186/s12916-024-03359-2.
- Li, Z. et al. (2025) 'Advancements in extracellular vesicles biomanufacturing: a comprehensive overview of large-scale production and clinical research', Frontiers in Bioengineering and Biotechnology, 13(February), pp. 1–19. doi:10.3389/fbioe.2025.1487627.
- Liu, J.J.J. et al. (2025) 'Exosomes in cancer nanomedicine: biotechnological advancements and innovations', Molecular Cancer, 24(1). doi:10.1186/s12943-025-02372-0.
- Lu, M. et al. (2023) 'Extracellular vesicle-based nucleic acid delivery', Interdisciplinary Medicine, 1(2). doi:https://doi.org/10.1002/INMD.20220007.
- Rezaie, J., Feghhi, M. and Etemadi, T. (2022) 'A review on exosomes application in clinical trials: perspective, questions, and challenges', Cell Communication and Signaling, 20(1), pp. 1–13. doi:10.1186/s12964-022-00959-4.
- Wang, Y. et al. (2025) 'Extracellular vesicles: From large-scale production and engineering to clinical applications'. doi:10.1177/20417314251319474.

Vijetha Karen Kitchley
International PhD Program in Cell Therapy and Regenerative Medicine,
Taipei Medical University

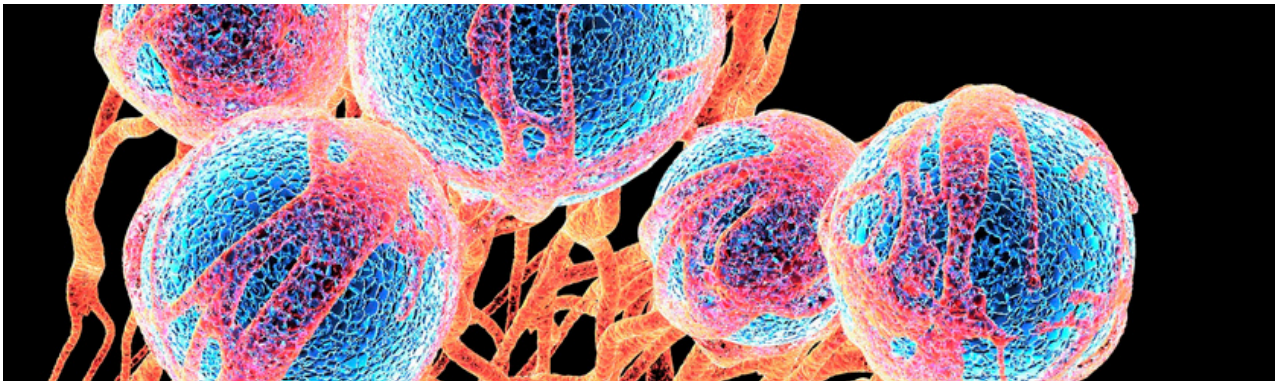


IMAGE FROM CANVA.COM

Role of Exosomes in Cancer: Molecular Mediator of Oncogenic Signaling and Microenvironmental Modulation

Mechanistic Overview of the Immune Evasion, Angiogenesis and Diagnostic Applications in Cancer

Introduction

Exosomes are nano-sized extracellular vesicles (30–150 nm) encapsulated by a phospholipid bilayer and secreted by both prokaryotic and eukaryotic cells to facilitate intercellular communication and molecular signaling (Fig. 1) [1]. Initially thought to function solely as cellular waste disposal vehicles, exosomes are now recognized as vital mediators of intercellular transport, delivering proteins, metabolites, and nucleic acids to various tissues [2, 3].

The formation of exosomes involves a multi-step process along the endosomal pathway. It begins with endocytosis, during which the plasma membrane invaginates to form early endosomes. These later mature into late endosomes [1]. During this maturation, cytoplasmic components such as proteins, lipids, and nucleic acids are sequestered into intraluminal vesicles (ILVs). These vesicles may then either fuse with the plasma membrane to release exosomes into the extracellular environment or be targeted for degradation via lysosomes if their contents are deemed non-essential [2].

Role of Exosomes in Cancer

Tumor Microenvironment (TME)

Exosomes significantly contribute to cancer development by modulating the tumor microenvironment (TME), largely through intercellular signaling. The bioactive molecules within exosomes are crucial for reprogramming the TME to favor tumor growth and progression [4]. For example, delta-like 4 protein (DLL4), transported via exosomes, induces angiogenic sprouting and enhances tumor aggressiveness in colorectal cancer [5, 6].

Tissue-specific targeting of exosomes is partly mediated by integrins, which are also involved in establishing the pre-metastatic niche and organ-specific metastasis in breast cancer [7]. Moreover, exosomal TGF-β promotes the differentiation of fibroblasts and mesenchymal stem cells into myofibroblasts, enhancing proliferation and invasiveness in prostate cancer [8, 9].

The TME is composed of various cellular constituents—endothelial cells, fibroblasts, immune cells—that collectively influence tumor progression [10]. Tumor-derived exosomes (TDEs) play a central role in regulating immune cell recruitment and function within this environment [11]. TDEs modulate the differentiation and activity of key immune cells, including NK cells, macrophages, T-cells, and B-cells [12]. Furthermore, exosomes from cancer cells can activate stromal fibroblasts into cancer-associated fibroblasts (CAFs), promoting metastasis and tumor invasion [13].

Angiogenesis

Angiogenesis, the formation of new blood vessels, is crucial for tumor expansion and the development of metastatic sites [14]. Numerous studies have demonstrated that exosomes enhance angiogenesis by transferring pro-angiogenic factors. In head and neck squamous cell carcinoma (HNSCC), TGF-β-enriched TDEs are instrumental in driving angiogenic processes within the TME [15]. In nasopharyngeal carcinoma, exosomes are rich in ICAM-1, CD44v5, and MMP-13, while anti-angiogenic proteins like TSP-1 are downregulated [16, 17]. Bladder cancer-derived exosomes have shown overexpression of EDIL-3, a protein critical for vascular development and angiogenesis [18].

Immune Modulation, Inflammation, and Evasion
Cancer cells often evade immune surveillance, and exosomes contribute significantly to this process. TDEs are key mediators of immunomodulation, influencing inflammatory responses and immune evasion. They transport cytokines and other small proteins that regulate inflammation and immune cell behavior. Chronic inflammation, often sustained by TDEs, suppresses cytotoxic T-cell activity and facilitates tumor progression [19, 20]. These vesicles can inhibit the differentiation and maturation of monocytes, contributing to an immunosuppressive microenvironment. This effect is largely dependent on exosomal proteins such as TGF-β, IL-6, and prostaglandin E2 (PGE2) [21]. IL-6 secreted via the PI3K/AKT/mTOR pathway also suppresses the differentiation of myeloid precursors in the bone marrow. Additionally, exosomal TGF-β1 can impair dendritic cell maturation [22].

Therapy Resistance
Exosomes have been implicated in modulating cell death pathways in recipient cells, thereby contributing to therapy resistance. These vesicles may originate from either viable or apoptotic cells. For example, fibroblast-derived exosomes containing membrane-bound TNF-α have been shown to suppress activation-induced cell death (AICD) in CD4+ T-cells [23], while exosomes bearing Fas ligand can trigger AICD in T-cells. In neuroblastoma, exosomes from N-myc-amplified cells enhance the survival of non-amplified cells by promoting resistance to doxorubicin [24]. In colorectal cancer, apoptotic vesicles released by tumor cells can induce T-cell apoptosis [25]. TDEs can also contain anti-apoptotic proteins such as survivin, XIAP, cIAP1, and cIAP2, helping cancer cells evade programmed cell death [26]. In bladder cancer, resistance is further reinforced by exosomal upregulation of Bcl-2 and cyclin D1, alongside the suppression of Bax and caspase-3 [27].

Diagnostic and Theranostic Applications
Accurate cancer diagnosis, risk assessment, and effective screening rely heavily on high-quality biomarkers. Tumor-derived exosomes have emerged as promising non-invasive diagnostic tools. Table 1 lists ongoing clinical trials evaluating exosomal proteins as biomarkers.

Conclusion
Exosomes participate in a wide range of biological processes essential to cancer progression, including extracellular matrix remodeling, angiogenesis, immune suppression, metastasis, and therapy resistance. Their cargo acts as a key communication tool within the TME and serves as a valuable source of biomarkers for cancer diagnosis, prognosis, and treatment. The utility of exosomes in liquid biopsies presents an alternative to traditional tissue biopsies. Ongoing research continues to uncover specific roles and mechanisms of exosomes in various cancer types, paving the way for more personalized and effective cancer therapies.

Table 1. Clinical trials focused on exosomal proteins as cancer biomarkers. [28]

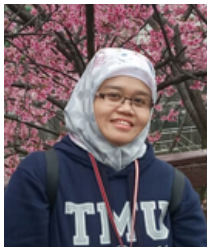
Number	Status	Cancer type	Exosomal content
NCT01840306	Completed	HER2 + Breast cancer	Not specified
NCT05463107	Not yet recrruiting	Follicular thyroid cancer	thyroglobulin Gal-3, calprotectin, A8/A9, keratin 8/19, afamin, angiopoietin-1
NCT02862470	Completed	Anaplastic Thyroid cancer	thyroglobulin, Gal-3
NCT04529915	Active	NSCLC	Not specified
NCT05735704	Recruiting	Haematological malignancies	Not specified
NCT03581435	Unknown	Gallbladder Carcinoma	Protein Profile
NCT03985696	Recruiting	Non-Hodgkin B-cell Lymphomas	CD-20, PD-L1

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. Tai Y, Chen K, Hsieh J, Shen T. Exosomes in cancer development and clinical applications. Cancer Sci. 2018;109:2364–74.
5. Sheldon H, et al. New mechanism for Notch signaling to endothelium at a distance by Delta-like 4 incorporation into exosomes. Blood. 2010;116:2385–94.
6. Zhang Z, et al. Delta-like ligand 4 level in colorectal cancer is associated with tumor aggressiveness and clinical outcome. Cancer Biomark Sect Dis Markers. 2022;33:415–22.
7. Hoshino A, et al. Tumour exosome integrins determine organotropic metastasis. Nature. 2015;527:329–35.
8. Webber J, Steadman R, Mason MD, Tabi Z, Clayton A. Cancer exosomes trigger fibroblast to myofibroblast differentiation. Cancer Res. 2010;70:9621–30.
9. Chowdhury R, et al. Cancer exosomes trigger mesenchymal stem cell differentiation into pro-angiogenic and pro-invasive myofibroblasts.Oncotarget. 2015;6:715–31.
10. Li I, Nabet BY. Exosomes in the tumor microenvironment as mediators of cancer therapy resistance. Mol Cancer. 2019;18:32.
11. Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contex- ture in human tumours: impact on clinical outcome. Nat Rev Cancer. 2012;12:298–306.
12. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nat Rev Immunol. 2009;9:581–93.
13. LeBleu VS, Kalluri R. A peek into cancer-associated fibroblasts: origins, functions and translational impact. Dis Model Mech. 2018;11:dmm029447.
14. Katayama Y, et al. Tumor neovascularization and developments in therapeutics. Cancers. 2019;11:316.
15. Ludwig N, Yerneni SS, Razzo BM, Whiteside TL. Exosomes from HNSCC promote angiogenesis through reprogramming of endothelial cells. Mol Cancer Res. 2018;16:1798–808.
16. Chan Y-K, et al. Proteomic analysis of exosomes from nasopharyngeal carcinoma cell identifies intercellular transfer of angiogenic proteins. Int J Cancer. 2015;137:1830–41.
17. You Y, et al. Matrix metalloproteinase 13-containing exosomes promote nasopharyngeal carcinoma metastasis. Cancer Sci. 2015;106:1669–77.
18. Beckham CJ, et al. Bladder cancer exosomes contain EDIL-3/Del1 and facilitate cancer progression. J Urol. 2014;192:583–92.
19. Lim S-O, et al. Deubiquitination and stabilization of PD-L1 by CSN5. Cancer Cell. 2016;30:925–39.
20. Grinberg-Bleyer Y, Ghosh S. A novel link between inflammation and cancer. Cancer Cell. 2016;30:829–30.
21. Yu S, et al. Tumor exosomes inhibit differentiation of bone marrow dendritic cells1. J Immunol. 2007;178:6867–75.
22. Wang M, Zhang B. The immunomodulation potential of exosomes in tumor microenvironment. J Immunol Res. 2021;2021:e3710372.
23. Zhang H-G, et al. A membrane form of TNF-α presented by exosomes delays T cell activation-induced cell death1. J Immunol. 2006;176:7385–93.
24. Sanwlani R, Gangoda L. Role of extracellular vesicles in cell death and inflammation. Cells. 2021;10:2663.
25. Huber V, et al. Human colorectal cancer cells induce T-cell death through release of proapoptotic microvesicles: role in immune escape. Gastroenterology. 2005;128:1796–804.
26. Valenzuela MMA, et al. Exosomes secreted from human cancer cell lines contain Inhibitors of Apoptosis (IAP). Cancer Microenviron Off J Int Cancer Microenviron Soc. 2015;8:65–73.
27. Yang L, Wu X-H, Wang D, Luo C-L, Chen L-X. Bladder cancer cell-derived exosomes inhibit tumor cell apoptosis and induce cell proliferation in vitro. Mol Med Rep. 2013;8:1272–8.
28. Hánělová, K., Raudenská, M., Masařík, M. et al. Protein cargo in extracellular vesicles as the key mediator in the progression of cancer. Cell Commun Signal 22, 25 (2024).

Editorial Team

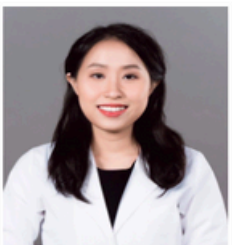
The ACTO Times
Asian Cellular Therapy Organization



Dyah Ika K, PhD
Associate professor
Surabaya

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

The ACTO Times

Asian Cellular Therapy Organization

CALL FOR ARTICLES

Spotlight :

- **Fall: South Korea, Vietnam**
- **Winter (New Year Edition): Iran**

Scope :

Regional CGT regulation, Clinical and Industry, Engineering CGT.

Deadline for Submission :

- **Fall: 15 September 2025**
- **Winter (New Year Edition): 15 December 2025**

The ACTO Times

Asian Cellular Therapy Organization

CALL FOR DONATION

CONTACT US

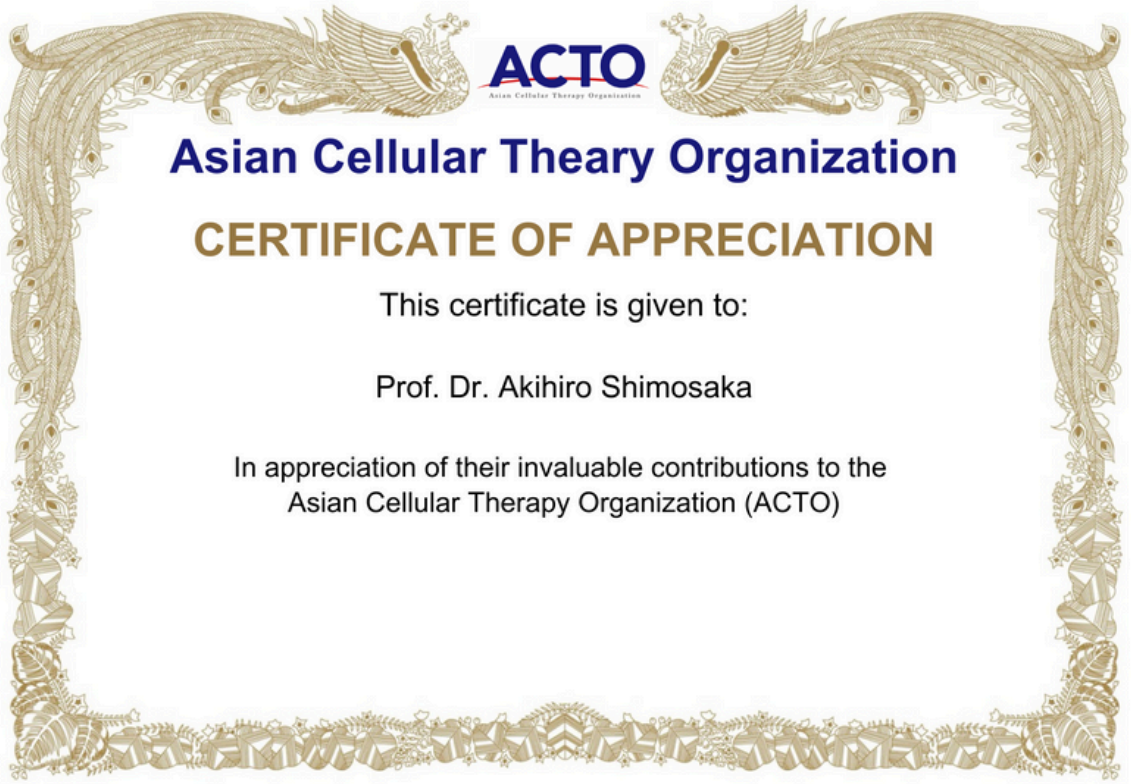
PROF. RITA YEN-HUA HUANG

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 SUMMER EDITION