

# The ACTO Times

Asian Cellular Therapy Organization

VOL. 03  
ISSUE 03  
E-ISSN 3105-6539  
[theactotimes.com](http://theactotimes.com)



**REGIONAL CGT  
REGULATION**

China & South Korea

**ACTO 2026  
JAKARTA**

The 17<sup>th</sup> Annual Meeting

**ACADEMIC READING,  
CGT INDUSTRY, &  
SPECIAL EDITION**

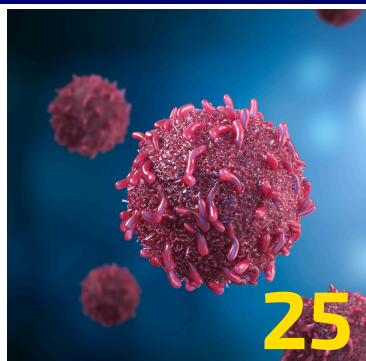
Immunology, Stem Cell Product,  
AI & CGT Clinical Trials

**2026 SUMMER  
EDITION**



# 2026 SUMMER EDITION

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# Greetings

## The ACTO Chairperson

THE ACTO TIMES  
2026 SUMMER EDITION



Dear ACTO members and readers,

It is our great pleasure to distribute ACTO Times 2026 Summer Version today. We are grateful to Prof. Huang and the ACTO Times editorial office team members who made it possible again.

We are expecting the 17<sup>th</sup> ACTO Annual Meeting in Jakarta, supported by Indonesia Ministry of Health. We are able to organize an attractive program arranged by Jakarta meeting organizing team. We will have an additional session focused on regulatory practical matters, especially for those in regulatory agencies. Regulatory Committee members, under the guidance of Dr. Maruyama, will help those who are starting new regulations for cell and gene therapy.

We will have the following ACTO annual meeting in Niigata, Japan, August 19~21, 2027, under the guidance of Prof. Shuji Terai, Niigata University. Please be ready to submit your abstract and be ready for presentation in Niigata. We would like to welcome your publication, overview, and opinion to be published on ACTO Times. Prof. Huang, Editor-in-Chief, will help with your publication.

We welcome you to share ACTO Times with your friends/colleagues and encourage them to become a member of ACTO. We have a Vice President in each country who represents ACTO. You are welcome to contact them for any advice related to ACTO activities. Also, you will be able to find past ACTO Annual Meeting presentations via the ACTO Website. You will have access when you contact ACTO HQ for help.

ACTO is an organization for those in the field of cell and gene therapy in Asia and any area who are interested in this field of research and development. Our members are from academia, industry, and regulatory agencies to work together for patients. The majority of Cell and Gene therapy uses patient cells, not for multiple patient use. We need regulations based on a new concept to control autologous therapy; conventional regulation is to control commercial products for distribution. Safety standards are different for autologous cell therapy. There are many patients who need cell and gene therapy. Harmonized regulation is important for those patients to be able to receive new therapy in their home country. ACTO will work for harmonization and provide opportunities for key players, academia, industry, and regulatory agencies to share information and discuss freely for the development of new therapy. All three payers are equally responsible for the development of new therapy.

We welcome your participation in ACTO activities.

Best regards,

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

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# Editor's Column

## The ACTO Times Editor-in Chief

THE ACTO TIMES  
2026 SUMMER EDITION

Dear Readers and Friends of The ACTO Times,

It is my great pleasure to welcome you to the 2026 Summer Edition of The ACTO Times. As we enter the summer season and prepare for the upcoming 2026 ACTO-ASPI Annual Meeting, to be held on August 26–28 in Jakarta, Indonesia, this issue arrives at a timely moment, bringing together important updates on the latest advances in cell and gene therapy (CGT), along with highlights from our symposium program.

In this edition, we warmly invite you to join us at the 2026 ACTO-ASPI International Annual Meeting in Jakarta, Indonesia. This gathering will provide an excellent opportunity to engage with the latest global developments in CGT, experience a dynamic scientific program, and meet a distinguished group of speakers and chairpersons. We are honored to welcome ACTO Chairperson Prof. Akihiro Shimosaka, Conference Chairperson Prof. Amin Soebandrio W. Kusumo, Republic of Indonesia Minister of Health H.E. Budi Gunadi Sadikin, Prof. Dr. Arif Satria, Prof. Masayo Takahashi, Prof. Koji Eto, Prof. Masato Sato, Prof. Keiya Ozawa, Dr. Maria Cristina Galli, Dr. Yoshiaki Maruyama, Prof. Taruna Ikrar, and Mr. Yueh-Tung Tsai.



This issue also highlights important regional developments in CGT across China and South Korea. In particular, we examine the evolving regulatory landscape, including the movement toward dual-track frameworks and the emergence of new legal pathways that are shaping the future of the field.

Our Academic Highlights focus on major advances in immunology and translational medicine, especially the 2026 Tang Prize Laureates in Biopharmaceutical Science, important milestones in T-cell-based therapies for cancer and autoimmune diseases, and emerging insights into the plasticity of neutrophils in cancer biology. In recognition of the twentieth anniversary of induced pluripotent stem cell (iPSC) research, this issue also features the recent conditional approval of two new allogeneic iPSC-based products, Amchepry (raguneprocel) and ReHeart. These landmark developments underscore the growing maturity and promise of regenerative medicine.

We also place special emphasis on the expanding role of artificial intelligence in drug development, digital biology, and cell therapy. Beyond cell product innovation, this edition turns to gene therapy clinical trials, an increasingly important area for understanding how gene editing may contribute to the treatment of rare diseases and for reviewing the latest progress in the field.

In addition, we spotlight developments in the CGT industry, with particular attention to the clinical applications of mesenchymal stem cells and immune cell CDMO services. The integrated translational framework and MSC product development efforts of UnicoCell Biomed Co., Ltd. (向榮生醫科技股份有限公司) and Steminent Biotherapeutics Inc. (仲恩生醫科技股份有限公司) are highlighted, alongside an overview of China's evolving CAR-T and immune cell therapy CDMO landscape.

I hope this Summer Edition provides you with an insightful and inspiring overview of the latest progress in CGT. Once again, we sincerely invite you to join us at the 2026 ACTO-ASPI Meeting in Jakarta. We look forward to welcoming you there and to sharing this exciting occasion together.

Sincerely,

A handwritten signature in blue ink, appearing to read 'Yen Hua Huang'.

**Yen Hua Huang, Ph.D.**

Editor-in-Chief, The ACTO Times

ACTO, Asian Cellular Therapy Organization

Distinguished Professor

College of Medicine, Taipei Medical University



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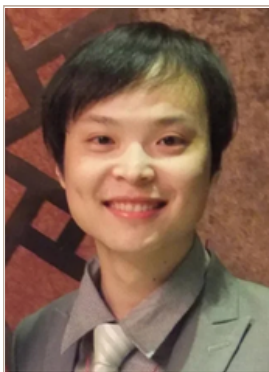
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**Yung-Che Kuo, Ph.D.**  
Taipei

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, Ph.D.**  
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.



**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.



**Nova, MD, Ph.D.**  
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.



**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.



**Yu-Xiu Lin, M.Sc**  
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.



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Asian Cellular Therapy Organization

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#### Editor in Chief

Prof. Yen-Hua Huang, Ph. D.



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- [theactotimes@gmail.com](mailto:theactotimes@gmail.com)
- [at.chiefeditor@gmail.com](mailto:at.chiefeditor@gmail.com)
- [editor@acto-hq.org](mailto:editor@acto-hq.org)





# 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

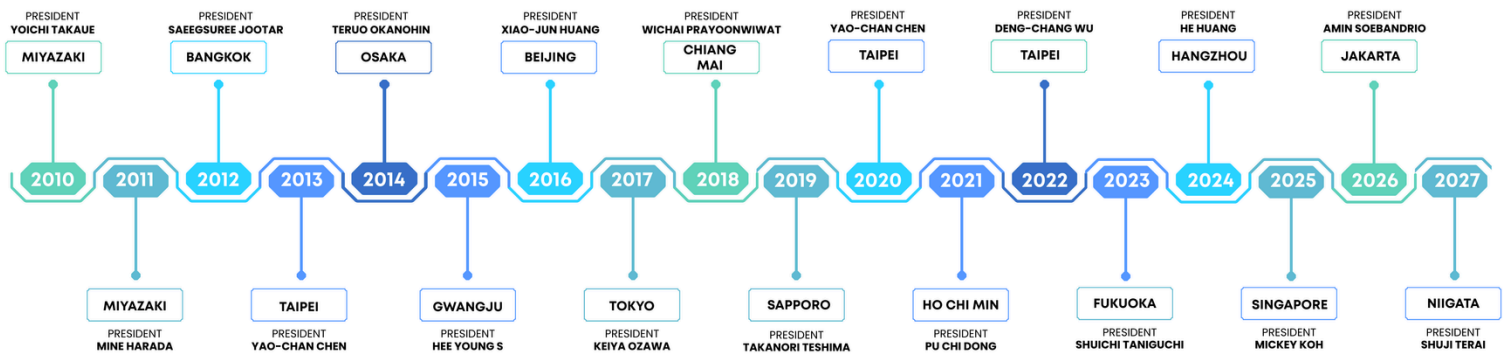
The diverse regulatory frameworks and rich cultural tapestry across Asian regions stand as influential forces shaping the intricate process of CGT in the region. In navigating this dynamic landscape, each nation brings its own set of regulations, reflecting unique perspectives on ethical considerations,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





# OUR JOURNEY THROUGH TIME

IMAGE FROM CANVA.COM



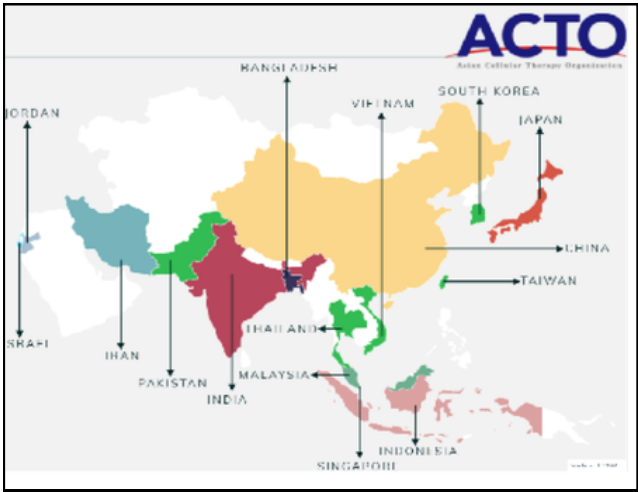
Over the years, the ACTO meetings became a cornerstone for professionals in the field, providing a platform for networking, sharing knowledge, and forging international partnerships. As the organization evolved, reflecting the dynamic landscape of CGT in the Asia-Pacific region.

The ACTO meeting was started from the first International Society of Cellular Therapy (ISCT) Asia-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.



## ACTO & Indonesia National Leadership

### Prof. Akihiro Shimosaka, PhD

#### Chairperson, Asian Cellular Therapy Organization

Prof. Akihiro Shimosaka is Chairperson of the Asian Cellular Therapy Organization and Director of the Research and Development Division at the Research Foundation for Community Medicine in Japan. He has extensive international experience in biotechnology research, product development and regulatory affairs, with particular interests in cellular immunotherapy, regenerative medicine, gene therapy and extracellular vesicles. Through ACTO, he has played an important role in strengthening scientific and regulatory collaboration in cellular therapy across Asia.



### Prof. Amin Soebandrio W. Kusumo, MD, PhD, SpMK(K)

#### President, ACTO–ASPI Annual Meeting Jakarta 2026

Prof. Amin Soebandrio is Professor of Clinical Microbiology at the Faculty of Medicine, Universitas Indonesia, and a leading Indonesian specialist in infectious diseases, molecular biology and stem-cell policy. He has served as Chair of the Indonesian Ministry of Health Committee for Stem Cell Development and previously led the Eijkman Institute for Molecular Biology. His scientific and public-health work has encompassed emerging infectious diseases, antimicrobial resistance, biosecurity and the responsible development of stem-cell technologies in Indonesia

### H.E. Budi Gunadi Sadikin

#### Minister of Health, Republic of Indonesia

Budi Gunadi Sadikin is the Minister of Health of the Republic of Indonesia. Appointed in December 2020, he has led Indonesia's national health transformation agenda, encompassing primary and referral care, health-system resilience, financing, healthcare human resources, and health technology. Before entering the health ministry, he served as Indonesia's Deputy Minister of State-Owned Enterprises and held senior leadership positions in the banking and state-owned enterprise sectors, including President Director of Bank Mandiri and PT Indonesia Asahan Aluminium. His ministerial leadership has emphasized preventive healthcare, digital health integration, expanded immunization, and the development of a more accessible and resilient national healthcare system.



### Prof. Dr. Arif Satria, S.P., M.Si.

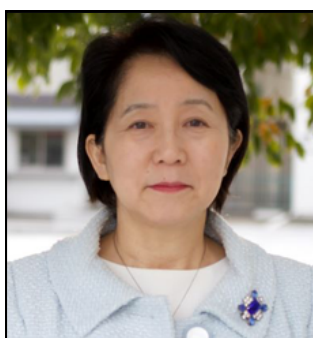
#### Head of National Research & Innovation Agency (BRIN) Indonesia

Prof. Dr. Arif Satria, S.P., M.Si., is Head of Indonesia's National Research and Innovation Agency (BRIN). Previously Rector of IPB University, he has extensive experience in academic leadership, research governance and national innovation policy. He earned his doctorate in marine policy from Kagoshima University, Japan. His expertise encompasses marine and fisheries policy, rural sociology and sustainable development. At BRIN, he leads efforts to align research and innovation with Indonesia's strategic development priorities.





## Clinical & Scientific Pioneer



### **Prof. Masayo Takahashi, MD, PhD**

#### **President and CEO, Vision Care Inc. and VC Cell Therapy Inc.**

Prof. Masayo Takahashi is an ophthalmologist and internationally recognized pioneer of retinal regenerative medicine. She is President and CEO of Vision Care Inc. and VC Cell Therapy Inc., a RARA Fellow at Ritsumeikan University and Senior Adviser at the Research Center of Kobe City Eye Hospital. After training at Kyoto University and the Salk Institute, she led retinal-regeneration research at RIKEN and conducted the landmark first clinical research using iPS cell-derived retinal cells in 2014.

### **Prof. Koji Eto, MD, PhD**

#### **Director of Center for iPS Cell Research and Application, Kyoto University**

Prof. Koji Eto, MD, PhD, is Director and Professor at the Center for iPS Cell Research and Application (CiRA), Kyoto University. A physician-scientist specializing in hematology and regenerative medicine, he leads research translating human induced pluripotent stem cells into next-generation blood products. His team conducted the world's first clinical study of autologous iPSC-derived platelet transfusion in a patient with platelet-transfusion refractoriness. His current work focuses on scalable production of iPSC-derived platelets and erythrocytes and their safe clinical application.



### **Prof. Masato Sato, MD, PhD**

#### **Professor, Department of Orthopaedic Surgery, Tokai University School of Medicine**

#### **Director, Center for Musculoskeletal Innovative Research and Advancement, Tokai University**

Prof. Masato Sato, MD, PhD, is Professor of Orthopaedic Surgery at Tokai University School of Medicine and Director of the Center for Musculoskeletal Innovative Research and Advancement. He is a leading expert in musculoskeletal regenerative medicine, with a focus on cartilage repair, tissue engineering, and cell-sheet technology for knee osteoarthritis. His pioneering work on autologous chondrocyte cell-sheet transplantation has contributed significantly to the clinical development of joint-preserving regenerative therapies in Japan.

### **Prof. Kei-ya Ozawa, MD, PhD**

#### **Professor Emeritus and Visiting Professor, Jichi Medical University, Japan**

Prof. Kei-ya Ozawa, MD, PhD, is Professor Emeritus and Visiting Professor at Jichi Medical University, Japan, and an Honorary Member of the Japan Society of Gene and Cell Therapy. He is a pioneering physician-scientist in gene therapy, with extensive expertise in adeno-associated virus vectors, hematopoietic stem-cell gene therapy and genetically engineered immune-cell therapies. His research has contributed to the development of CD19-directed CAR-T-cell therapy and innovative regulatory gene systems designed to improve the safety and controllability of therapeutic cells.





## Global Regulatory Authorities



### **Dr. Maria Cristina Galli, PhD**

#### **Former European Medicines Agency (EMA) regulatory expert**

Dr. Maria Cristina Galli is a regulatory-science specialist with extensive experience in advanced therapy medicinal products, including gene therapies, cell therapies and tissue-engineered products. She holds qualifications in biological sciences and molecular medicine and previously served as a senior researcher at the Istituto Superiore di Sanità in Rome. She was formerly a member of the European Medicines Agency's Committee for Advanced Therapies and Chair of the EMA Gene Therapy Working Party. She currently works as an independent consultant in gene- and cell-therapy development and manufacturing.

### **Dr. Yoshiaki Maruyama, PhD**

#### **Director, Office of Cellular and Tissue-based Products, Pharmaceuticals and Medical Devices Agency (PMDA), Japan**

Dr. Yoshiaki Maruyama is Director of the Office of Cellular and Tissue-based Products at Japan's Pharmaceuticals and Medical Devices Agency. Since joining PMDA in 2008, he has worked in pharmaceutical standards, product evaluation and regulatory science. His responsibilities encompass the review and post-marketing oversight of cell and gene therapies, tissue-based products and biological products, giving him extensive experience in Japan's regulatory pathways for regenerative medical products.



### **Prof. Taruna Ikrar, MD, M.Biomed, PhD**

#### **Head of the Indonesian Food and Drug Authority (BPOM)**

Prof. Taruna Ikrar is Head of Indonesia's National Agency of Drug and Food Control, BPOM, a position he has held since August 2024. He is a physician and biomedical scientist whose work integrates pharmacology, cardiovascular science and neuroscience. He earned his medical degree from Universitas Hasanuddin, a master's degree from Universitas Indonesia and a PhD from Niigata University, followed by postdoctoral research at the University of California, Irvine. His research experience includes functional imaging and cell- and gene-based approaches for rare diseases.

### **Mr. Yueh-Tung Tsai, BPharm, MHWP**

#### **Technical Specialist, Division of Medicinal Products, Taiwan Food and Drug Administration (TFDA)**

Mr. Yueh-Tung Tsai is a Technical Specialist in the Division of Medicinal Products at the Taiwan Food and Drug Administration. He graduated in pharmacy from Taipei Medical University and received a master's degree in health and welfare policy from National Yang Ming Chiao Tung University. Since joining TFDA in 2013, he has contributed to medicinal-product evaluation and regulatory activities, including the regulation and review of regenerative-medicine products in Taiwan.

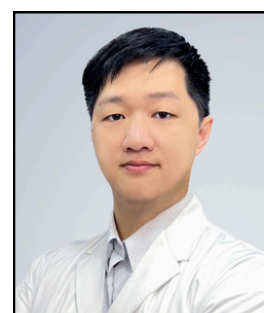






IMAGE FROM CANVA.COM

## China's Evolving Regulatory Framework for Cell and Gene Therapies: From Dual-Track Oversight to a New Legal Phase

### Abstract

China has developed one of the world's most active cell and gene therapy research environments, accompanied by a regulatory system that has evolved rapidly over the past decade. The framework has often been described as "dual-track," comprising a drug-product pathway administered by the National Medical Products Administration and a medical-technology or investigator-initiated research pathway overseen primarily by health authorities. However, these pathways should not be understood as interchangeable routes for the same product. Standardized cell and gene therapy products intended for commercial development are generally regulated as drugs, whereas the technology pathway is intended for specified biomedical innovations that do not appropriately fit conventional product development. A major transition occurred with the promulgation of the Administrative Regulation on Clinical Research and Clinical Translation of New Biomedical Technologies, which entered into force on May 1, 2026. The regulation establishes legally binding requirements for research filing, institutional qualification, ethical review, participant protection, clinical translation, long-term follow-up, supervision, and liability. This review summarizes the development of China's cell and gene therapy regulation, clarifies the relationship between the product and technology pathways, and identifies areas requiring continued regulatory development.

**Keywords:** cell therapy; gene therapy; China; regulation; clinical research; advanced therapy medicinal products

### Introduction

Cell and gene therapies encompass a diverse group of interventions, including immune-cell therapies, stem-cell products, genetically modified cells, in vivo gene therapies, and other technologies acting at the cellular or molecular level. Their potential clinical benefits are accompanied by distinctive risks, including product variability, manufacturing complexity, insertional mutagenesis, prolonged biological activity, immune toxicity, tumorigenicity, and uncertain long-term outcomes. Regulatory oversight must therefore address not only conventional clinical safety and efficacy but also source materials, manufacturing consistency, potency, traceability, long-term monitoring, and institutional capability.

China's cell therapy sector has expanded considerably, particularly in chimeric antigen receptor T-cell therapy, stem-cell research, and investigator-initiated clinical studies. Published analyses describe China as having a dual-track regulatory framework that supports both industry-sponsored drug development and institution-based clinical research [1–4].

Nevertheless, the expression "dual-track" can oversimplify the system. The two pathways have different legal objectives, evidentiary requirements, responsible authorities, and routes to clinical use. They should not be presented as parallel commercial options from which a developer may freely select.

### Evolution of the regulatory framework

Earlier Chinese regulation of cell therapy developed through a combination of medical-technology administration and drug regulation. Institution-based research was particularly important for stem-cell and immune-cell interventions. In 2015, the former National Health and Family Planning Commission and the China Food and Drug Administration jointly issued the Administrative Measures for Stem Cell Clinical Research (Trial). These measures established institutional and project-filing requirements for stem-cell research and placed primary responsibility for research quality and participant protection on qualified medical institutions [5].

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A more explicit product pathway emerged through the 2017 Technical Guideline for Research and Evaluation of Cell Therapy Products (Trial). The guideline applies to human living-cell products developed and submitted for registration as drugs and sets general expectations for risk control, pharmaceutical development, nonclinical studies, and clinical evaluation [6]. It does not apply automatically to every clinical use of cells and expressly distinguishes drug-registration development from cell technologies managed under other pathways.

China subsequently issued more specialized technical guidance. These documents address clinical trials of immune-cell therapy products, nonclinical evaluation of gene therapy products, nonclinical studies of genetically modified cell therapies, in vivo gene therapy manufacturing, communication with regulators, and clinical pharmacology considerations [7,8]. The expanding guidance system reflects increasing recognition that cell and gene therapies cannot be evaluated adequately using requirements designed only for conventional small-molecule medicines.

Peer-reviewed documentary analysis has found that China has progressively developed regulatory functions covering clinical-trial authorization, marketing authorization, laboratory testing, inspection, licensing, and pharmacovigilance for advanced therapies [2,3]. However, researchers have also identified areas requiring further refinement, including greater coordination among regulatory functions, consistent implementation of technical standards, transparency, investigator-initiated research quality, and product-specific post-marketing surveillance [2–4,9].

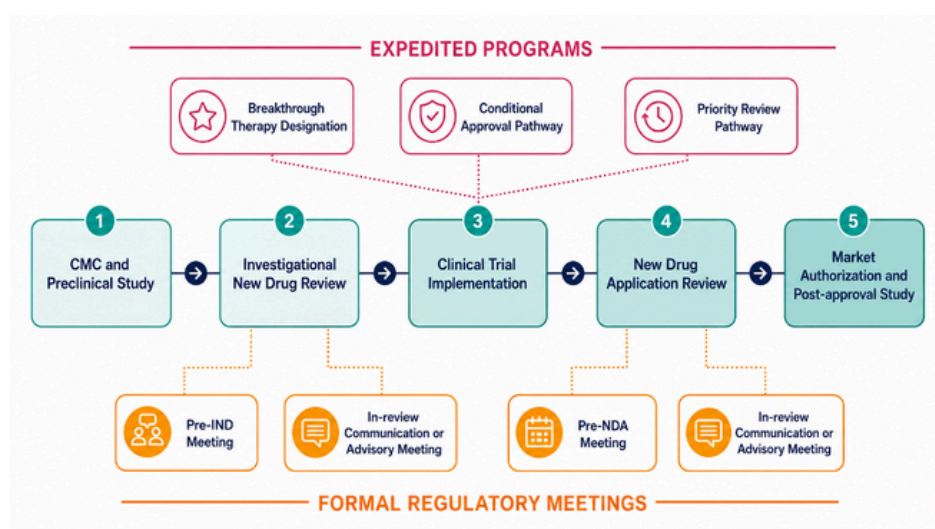
### The drug-product pathway

Cell and gene therapy candidates that possess a defined product form and are intended for standardized, reproducible, and potentially scalable production are generally developed under the drug regulatory pathway. The National Medical Products Administration, principally through its Center for Drug Evaluation, is responsible for the technical review of clinical-trial and marketing applications.

Under this pathway, the sponsor develops a defined investigational product and submits evidence on manufacturing, quality control, nonclinical safety, and the proposed clinical investigation. Product characterization may include identity, purity, viability, potency, genetic stability, vector-related attributes, sterility, adventitious-agent control, and comparability following manufacturing changes. The precise requirements depend on the nature of the therapy and are applied on a case-by-case basis [2,6–8].

Clinical development is conducted under the drug-registration system and must comply with applicable requirements for good clinical practice. Successful development may lead to national marketing authorization. Once authorized, the product remains subject to manufacturing supervision, pharmacovigilance, risk management, change control, and other life-cycle requirements.

China's product pathway has supported substantial growth in industry-sponsored cell therapy trials and the authorization of several cellular immunotherapies.



**Figure 1.** The review pathway for advanced therapy medicinal products (ATMPs) covers the full development lifecycle, beginning with chemistry, manufacturing, and controls (CMC) and preclinical evaluation, followed by investigational new drug (IND) review, clinical trial conduct, new drug application (NDA) assessment, marketing authorization, and post-approval studies. Common expedited regulatory mechanisms include priority review, breakthrough therapy designation, and conditional approval. Formal interactions with regulatory authorities typically occur through pre-IND and pre-NDA meetings, while additional in-review discussions or advisory meetings may be arranged when further clarification is required [2].



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Nevertheless, most registered cell therapy studies in China have historically been investigator-initiated rather than industry-sponsored. An analysis covering clinical trials through August 2024 identified 2,794 cell therapy studies, of which approximately 90% were categorized as investigator-initiated trials [4]. The authors noted that these studies can generate useful exploratory evidence but may vary in manufacturing control, study design, data quality, and their suitability for supporting subsequent drug applications.

Post-marketing regulation is particularly important for therapies whose effects may persist for months or years. A comparative study published in 2024 concluded that China had introduced several relevant post-marketing requirements for cell and gene therapy products, but that dedicated guidance was less detailed than the corresponding systems examined in the European Union, United States, Japan, and South Korea [9]. This conclusion represents the situation assessed by the authors before implementation of the 2026 biomedical-technology regulation and should not be interpreted as an evaluation of the new framework.

### The biomedical new-technology pathway

The most significant recent development is the Administrative Regulation on Clinical Research and Clinical Translation of New Biomedical Technologies, promulgated as State Council Order No. 818 and effective from May 1, 2026 [10]. It provides a statutory framework for clinical research and clinical translation of biomedical technologies that apply biological principles, act at the human cellular or molecular level, and have not yet been clinically applied in China.

Importantly, the regulation does not replace the drug or medical-device systems. Article 55 states that clinical trials undertaken to develop drugs or medical devices remain governed by the Drug Administration Law, the medical-device regulations, and related legislation [10]. The National Health Commission and National Medical Products Administration have consequently emphasized that institutions should select either the biomedical-technology pathway or the drug/device pathway according to the nature and intended development of the intervention [11].

Official implementation guidance further narrows the scope of technologies eligible for clinical translation through the new pathway. A technology must be included in the relevant clinical-research filing guidance list and generally must meet at least one of two conditions: it is highly individualized and no drug based on a similar mechanism has obtained domestic marketing authorization or entered a confirmatory clinical trial; or it treats a rare disease for which no drug with a similar mechanism and the same indication has obtained authorization or entered a confirmatory trial [12]. Technologies meeting the legal definition of a medical device are excluded from this clinical-translation route.

The distinction is therefore not simply “commercial trial versus hospital trial.” Technologies that already have an evident product form and can be standardized and manufactured at scale generally fall outside the biomedical-technology clinical-translation pathway. Moreover, data generated under the technology pathway are intended to support clinical translation of that technology, rather than automatically serving as a transitional stage toward drug marketing authorization [11,12].

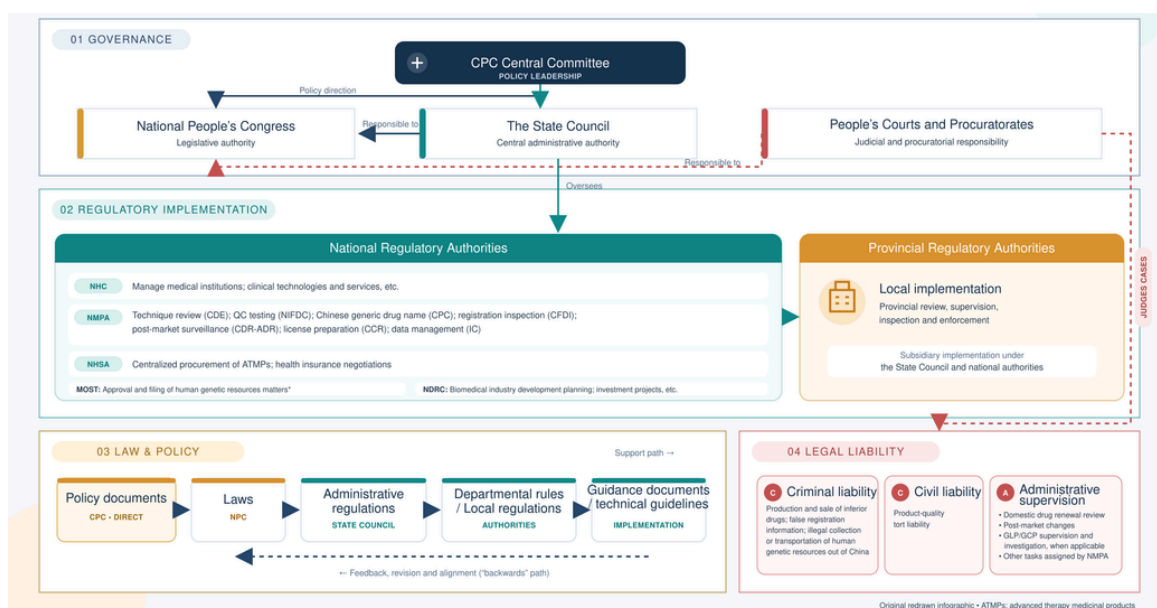


Figure 2. China's regulatory administration framework of ATMPs [3].

### Requirements for clinical research

Order No. 818 establishes specific institutional and procedural requirements. A clinical-research sponsor must be a legal person established in China, while the institution implementing the research must generally be a tertiary Grade A medical institution with qualified academic and ethics committees, appropriate facilities, trained personnel, research capability, management systems, and stable funding [10].

Before human research begins, sufficient laboratory and animal investigations must support the proposed technology. The research must undergo both academic and ethical review, after which the clinical institution must file the study with the national health authority within five working days. Filing is not equivalent to an unconditional authorization: the health authority may assess a filed project and require modification, suspension, or termination when technical or ethical risks are identified [10].

The regulation strengthens participant protections. Written informed consent is required, and information must be presented in a manner understandable to participants or their legal representatives. Sponsors and research institutions may not charge participants fees related to the clinical research. Research records and source materials must generally be retained for 30 years after completion; records involving offspring must be retained permanently. Serious adverse reactions may require suspension and ethical reassessment, and long-term follow-up is required to evaluate safety and effectiveness [10].

These provisions provide a more explicit legal basis for responsibilities previously addressed through trial measures, ethical rules, administrative guidance, and institutional requirements. They also introduce substantial administrative, financial, and professional penalties for unfilled research, unauthorized clinical application, failure to obtain informed consent, data falsification, and other violations.

### Clinical translation and controlled application

A biomedical new technology cannot enter routine clinical use solely because a filed research project has been completed. Clinical translation requires approval from the National Health Commission. The application must include the research report and records, proposed indications, adverse reactions, contraindications, institutional and professional qualifications, operating procedures, and risk-control measures [10].

The 2026 approval specification adds that the technology must have demonstrated safety, effectiveness, and ethical acceptability. It must also have been implemented independently in a multicenter setting according to a common operating procedure, with consistent safety and effectiveness conclusions [12].

This requirement is intended to demonstrate that the intervention is technically mature, reproducible, and not dependent exclusively on the expertise of a single institution.

Following approval, qualified medical institutions may apply the technology in accordance with the published operating requirements and may charge fees as permitted by applicable rules. Clinical application remains subject to reporting, risk management, surveillance, and re-evaluation. Approval can be suspended or withdrawn when new evidence changes the assessment of safety or effectiveness or when serious and uncontrollable risks emerge [10,12].

### Remaining challenges

The 2026 regulation addresses a long-standing need for a clearer legal pathway for highly individualized and institution-dependent biomedical technologies. It establishes enforceable requirements extending from clinical research to controlled clinical translation. Nevertheless, several issues will require observation as the system is implemented.

First, the practical boundary between a “technology” and a “product” may remain difficult for rapidly evolving or partially standardized interventions. Manufacturing models can change during development, and an initially individualized intervention may later become scalable. Continuous coordination between health and drug authorities will therefore be essential.

Second, filing should not be interpreted as a reduced scientific standard. Investigator-initiated studies must generate reliable, traceable, and clinically interpretable data. Published analyses have highlighted large differences between investigator-initiated and industry-sponsored cell therapy studies in China [4]. Strong protocol design, prospective registration, validated manufacturing controls, independent monitoring, transparent reporting, and appropriate statistical analysis remain necessary.

Third, long-term follow-up and post-application surveillance must be sufficiently detailed for therapies with persistent or irreversible effects. The collection of standardized long-term safety data, management of delayed adverse events, traceability of starting materials, and linkage between institutional and national safety systems will be especially important for gene-modified and stem-cell interventions [3,9].

Finally, the impact of Order No. 818 cannot yet be evaluated conclusively. The regulation entered into force only on May 1, 2026, and peer-reviewed literature published before that date necessarily describes the preceding system.

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Claims regarding improved efficiency, patient access, innovation, or safety should therefore be presented as regulatory objectives rather than established outcomes until implementation data become available.

### Conclusion

China's cell and gene therapy framework has progressed from fragmented oversight toward a more structured system combining product regulation with a legally defined biomedical-technology pathway. The drug pathway remains the principal route for standardized cell and gene therapy products intended for manufacturing and marketing. The new-technology pathway provides a separate route for selected highly individualized or rare-disease technologies that do not fit conventional product development.

The 2026 regulation should not be characterized as deregulation or as a general alternative to drug approval. It introduces institutional qualifications, filing, academic and ethical review, participant protections, long-term follow-up, approval before clinical translation, ongoing supervision, and significant legal liability. Its long-term significance will depend on clear classification, consistent implementation, high-quality clinical evidence, coordination between authorities, and transparent post-application monitoring.

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IMAGE FROM CANVA.COM

## South Korea's Regulatory Architecture for Cell and Gene Therapies: Linking Clinical Research, Regulated Treatment, and Product Authorization

### Abstract

South Korea has established a distinctive regulatory architecture for cell and gene therapies that links advanced regenerative medicine, institution-based clinical research, medicinal-product development, and long-term safety oversight. The central framework was introduced through the Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products, enacted in 2019 and implemented in 2020. The system distinguishes advanced regenerative medicine conducted within designated medical institutions from advanced biological products developed as standardized medicinal products. Clinical research is subject to risk-based review, institutional qualification, participant protection, and safety monitoring, while commercial cell and gene therapy products remain subject to manufacturing, clinical-trial, marketing-authorization, and post-marketing requirements. A major amendment implemented in February 2025 introduced advanced regenerative medicine treatment as a separate legal category, enabling selected interventions to be provided outside clinical research under reviewed treatment plans. This report summarizes the structure of the Korean framework, its expedited product-development mechanisms, post-marketing surveillance system, and continuing challenges related to evidence generation, patient access, affordability, and the distinction between regulated medical treatment and medicinal-product authorization.

**Keywords:** cell therapy; gene therapy; advanced regenerative medicine; advanced biological products; South Korea; regulation

### Introduction

Cell and gene therapies present regulatory challenges that differ substantially from those associated with conventional pharmaceutical products. Their clinical performance may be influenced by donor characteristics, cell source, genetic modification, manufacturing variability, storage, transport, administration procedures, and the clinical expertise of the treating institution. Potential risks may include immune toxicity, tumorigenicity, unintended genetic alterations, contamination, abnormal differentiation, and adverse effects that emerge long after treatment.

South Korea introduced a dedicated framework to support the development of these therapies while strengthening patient protection and long-term safety management. The Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products, frequently abbreviated in published literature as the ARMAB Act, was enacted in August 2019 and implemented in August 2020 [1,2].

The legislation consolidated several previously fragmented regulatory functions and created a legal distinction between advanced regenerative medicine and advanced biological products.

This distinction is fundamental. Advanced regenerative medicine concerns the clinical application of cell, gene, tissue-engineering, or convergence-based technologies within qualified medical institutions. Advanced biological products are developed as defined medicinal products and include cell therapy products, gene therapy products, tissue-engineered products, and advanced biological combination products [1,2]. Although both domains are addressed within the same legislative architecture, they follow different review pathways and should not be treated as interchangeable routes to clinical use.

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# SPOTLIGHT

## Regional CGT Update

*South Korea CGT Regulation*

### **An integrated but differentiated regulatory framework**

The Korean framework distributes responsibilities primarily between the Ministry of Health and Welfare and the Ministry of Food and Drug Safety. The Ministry of Health and Welfare is principally associated with the administration of advanced regenerative medicine in medical institutions, whereas the Ministry of Food and Drug Safety oversees advanced biological products, product clinical trials, manufacturing controls, marketing authorization, and post-authorization safety management [1,2,4].

Published analyses describe this structure as an integrated system with two connected regulatory domains. The first domain covers institution-based regenerative medicine, initially centred on clinical research and now also including a regulated treatment category. The second domain covers standardized products intended for manufacture, distribution, and commercial authorization [1–4].

The classification of an intervention cannot be determined merely by the presence of cells or genetic material. The intended mode of development, degree of manipulation, manufacturing model, clinical setting, and proposed distribution all influence whether an intervention is treated as advanced regenerative medicine or as an advanced biological product. This distinction becomes particularly important when an initially individualized hospital-based intervention develops into a reproducible and scalable product.

### **Advanced regenerative medicine clinical research**

Advanced regenerative medicine clinical research is intended to provide a controlled pathway for investigating regenerative interventions in patients while generating evidence on safety and clinical performance. Published descriptions of the Korean system indicate that such research must be conducted in designated medical institutions with appropriate facilities, personnel, governance, and safety-management capacity [1,2].

Research plans undergo centralized scientific and ethical evaluation. The review considers the scientific rationale, anticipated benefits, foreseeable risks, participant-selection criteria, study design, cell-processing procedures, and measures for managing adverse events. The framework applies a risk-based approach, with higher-risk studies receiving more extensive scrutiny. High-risk research requires an additional assessment by the Ministry of Food and Drug Safety after review by the relevant regenerative medicine review committee [1,4].

This system should not be interpreted as a reduced form of clinical-trial oversight. Regenerative medicine research remains subject to informed consent, protocol compliance, data integrity, adverse-event reporting, participant protection, and, where appropriate, long-term follow-up. The need for long-term monitoring is especially important for genetically modified cells, stem-cell-derived interventions, and products capable of persisting or proliferating after administration [1,2].

Clinical research also remains distinct from routine medical treatment. Under the original framework implemented in 2020, advanced regenerative medicine was primarily accessed through approved research protocols. The research pathway was designed to generate knowledge and evaluate safety and effectiveness rather than to permit unrestricted clinical provision of unproven interventions [1].

### **Introduction of advanced regenerative medicine treatment**

A major regulatory development occurred through an amendment that introduced advanced regenerative medicine treatment as a separate legal category. The amendment became effective in February 2025 and was subsequently examined in a 2026 peer-reviewed analysis by Yoon and colleagues [3].

The new treatment category creates a route through which selected advanced regenerative medicine interventions may be provided outside a clinical-research protocol. However, this pathway should not be characterized as general permission to offer unapproved cell or gene therapies. Treatment remains dependent on institutional qualification, review of the proposed treatment plan, safety-management arrangements, informed consent, and continuing oversight [3].

The distinction between clinical research and advanced regenerative medicine treatment is important. Clinical research is designed primarily to generate systematic evidence according to a research protocol. Advanced regenerative medicine treatment is provided as medical care under a reviewed treatment plan. Nevertheless, the introduction of a treatment pathway does not automatically establish the same level of evidence as conventional medicinal-product marketing authorization.

Similarly, approval of an institution-specific treatment plan does not mean that the underlying cells, vector, manufacturing process, or technology may be manufactured and distributed nationally as an authorized medicinal product. Commercial distribution remains subject to the separate advanced biological product pathway administered by the Ministry of Food and Drug Safety [3,4].

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# SPOTLIGHT

## Regional CGT Update

### *South Korea CGT Regulation*

The new treatment category is intended to improve access for patients with serious or difficult-to-treat conditions, but it also introduces regulatory and ethical questions. These include the level of evidence required before treatment, the consistency of review decisions, long-term follow-up, patient understanding of uncertainty, financial burden, and the prevention of therapeutic misconception [3]. Since the pathway only became operational in 2025, its effects on clinical outcomes, patient access, healthcare expenditure, and product development remain too recent for definitive evaluation.

#### **Advanced biological products and medicinal-product authorization**

Cell and gene therapies intended to be manufactured and marketed as standardized products are regulated as advanced biological products. This pathway follows the general lifecycle of medicinal-product development, including chemistry, manufacturing and controls, nonclinical studies, clinical-trial authorization, clinical development, marketing-authorization review, and post-approval surveillance [1,4].

Manufacturing control is particularly important because the clinical characteristics of a cell or gene therapy may be altered by relatively small changes in raw materials, cell culture, genetic modification, purification, cryopreservation, transport, or administration. Developers must therefore establish appropriate controls for identity, purity, viability, potency, sterility, genetic stability, donor eligibility, adventitious agents, and batch-to-batch consistency [4,6].

For gene-modified therapies, additional considerations may include vector design, biodistribution, persistence, off-target effects, insertional mutagenesis, shedding, immune responses, and the possibility of unintended germline exposure. Stem-cell-derived products may require careful assessment of differentiation status, residual undifferentiated cells, genetic abnormalities, tumorigenicity, and functional potency [5,6].

The Ministry of Food and Drug Safety evaluates the totality of manufacturing, nonclinical, and clinical evidence. Marketing authorization applies to a defined product, indication, manufacturing process, and conditions of use. It is therefore broader than approval of a treatment plan at an individual medical institution, but it also requires a more extensive and standardized evidence package.

#### **Expedited development and conditional approval**

South Korea has introduced expedited mechanisms for eligible advanced biological products intended to address serious, life-threatening, or rare diseases. The mechanisms described in the published literature include customized review, priority review, and conditional approval [1,4]. Customized review allows portions of the application to be evaluated progressively according to the developer's preparation schedule.

Priority review gives an eligible product precedence over standard applications. Conditional approval may permit earlier authorization on the basis of preliminary clinical evidence, with additional or confirmatory studies required after marketing [1,4].

These mechanisms are designed to reduce unnecessary delays where patients have substantial unmet medical needs. However, expedited development does not eliminate the requirements for manufacturing quality, clinical justification, risk management, or post-authorization evidence. Conditional approval transfers part of the evidentiary burden to the post-marketing period rather than removing that burden.

This approach can be particularly relevant to CGTs because conventional large, randomized trials may be difficult for rare diseases or highly individualized products. Nevertheless, reliance on smaller studies, surrogate endpoints, or early clinical outcomes increases uncertainty at the time of authorization. Effective post-marketing surveillance and timely completion of confirmatory studies are therefore essential.

#### **Post-marketing surveillance and long-term follow-up**

Long-term safety oversight is one of the most prominent elements of the Korean framework. The biological effects of cell and gene therapies may persist for years, and some complications may not be detected during the relatively limited duration of pre-authorization clinical trials [1,5].

The Korean system includes mechanisms for long-term follow-up, electronic safety reporting, traceability, periodic safety reporting, re-examination, and re-evaluation. A comparative study of post-marketing surveillance frameworks reported that South Korea's principal approaches for CGT products include periodic safety update reports, re-examination, and re-evaluation [5].

Long-term surveillance is particularly relevant for gene therapies, genetically modified cells, and stem-cell products. Monitoring should be capable of identifying delayed malignancy, persistent immune reactions, loss of therapeutic effect, abnormal tissue formation, or complications related to the administered cells or vector.

The effectiveness of post-marketing surveillance depends not only on formal requirements but also on the completeness and quality of the collected data. Patient retention, interoperability between databases, accurate product traceability, standardized adverse-event definitions, and coordination between medical institutions, manufacturers, and regulators remain important practical considerations [1,5].



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# SPOTLIGHT

## Regional CGT Update

### *South Korea CGT Regulation*

#### **Pricing, reimbursement, and patient access**

Regulatory authorization does not by itself guarantee patient access. CGTs are frequently associated with high manufacturing and treatment costs, small eligible populations, limited long-term evidence, and uncertainty regarding the duration of therapeutic benefit. These features create substantial challenges for health-technology assessment, pricing, and reimbursement [4].

South Korea's reimbursement system uses health-technology and economic assessments similar in several respects to those applied in European countries. Risk-sharing agreements may be used to manage financial and clinical uncertainty, particularly for high-cost therapies with limited evidence at launch [4].

However, different access questions arise under the advanced regenerative medicine treatment pathway. Institution-based treatment may improve access before a standardized product completes conventional development, but it can also transfer greater uncertainty or financial responsibility to patients. Clear communication is therefore needed regarding the difference between clinical research, regulated medical treatment, conditional product authorization, and full marketing authorization.

#### **Continuing challenges**

The first challenge is maintaining a clear boundary between institution-based treatment and commercial product development. A therapy may begin as an individualized intervention but later become reproducible and scalable. Regulators must determine when continued use under a treatment plan remains appropriate and when the intervention should proceed through the medicinal-product pathway.

The second challenge is evidentiary consistency. Different institutions may possess different manufacturing capabilities, clinical expertise, and follow-up systems. Standardized outcome measures, transparent review criteria, and common data-reporting requirements will be needed to compare treatment performance across institutions.

Third, patient expectations must be managed carefully. Individuals with serious or incurable diseases may interpret regulatory review as proof of established efficacy. Informed consent should therefore clearly communicate the maturity of the evidence, potential benefits, known and unknown risks, alternatives, financial obligations, and available compensation or follow-up arrangements [3].

Fourth, rapid technological development will continue to challenge existing classifications. Gene editing induced pluripotent stem-cell-derived therapies, decentralized manufacturing, automated cell-processing systems, and personalized products may not fit neatly within traditional distinctions between a medical procedure and a manufactured medicinal product [2,6].

Finally, international regulatory convergence remains important. Common terminology, manufacturing standards, long-term follow-up expectations, and evidence requirements could facilitate multinational trials and reduce duplication while maintaining patient protection [2,4,6].

#### **Conclusion**

South Korea has created an integrated regulatory architecture that recognizes the distinctive characteristics of cell and gene therapies while separating institution-based regenerative medicine from commercial medicinal-product development. The framework implemented in 2020 established risk-based clinical-research review, institutional qualification, expedited product-development mechanisms, and long-term safety monitoring.

The introduction of advanced regenerative medicine treatment in February 2025 represents an important expansion of this system. It provides a regulated route for selected interventions to be delivered outside clinical research, but it does not replace medicinal-product authorization or permit unrestricted clinical use of unproven CGTs.

The strength of the Korean model lies in its attempt to connect innovation, patient access, product regulation, and long-term safety within a coordinated framework. Its future credibility will depend on consistent evidence standards, clear separation of research, treatment, and commercialization, transparent patient communication, effective post-treatment surveillance, and careful evaluation of outcomes generated under the new treatment pathway.

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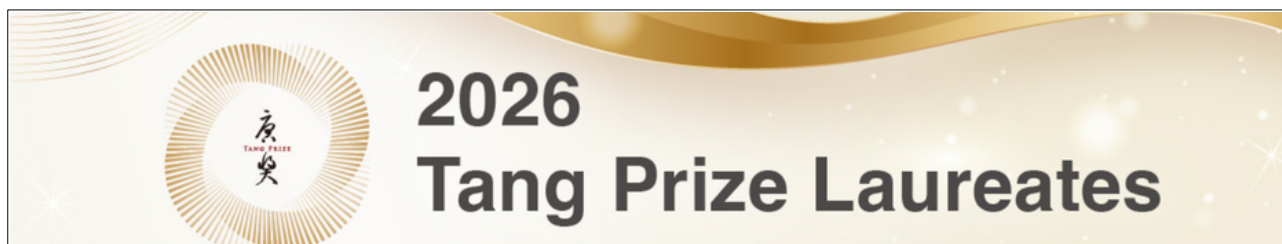


IMAGE FROM TANG-PRIZE.ORG

## Reimagining Cancer Treatment: The 2026 Tang Prize Laureates in Biopharmaceutical Science

**The 2026 Tang Prize** in Biopharmaceutical Science has been awarded jointly to Steven A. Rosenberg, Michel Sadelain, and Carl H. June for their groundbreaking contributions to the development of cellular immunotherapy, a revolutionary approach that enables a patient's own immune system to recognize and destroy cancer [1,2].

Established in Taiwan in 2012, the Tang Prize recognizes outstanding achievements in four categories: Sustainable Development, Biopharmaceutical Science, Sinology, and Rule of Law. The Biopharmaceutical Science Prize celebrates innovations that significantly improve human health through advances in biomedical research. Many Tang Prize laureates have later received Nobel Prizes, highlighting the award's growing international reputation [2].

### Revolutionizing Cancer Treatment

For decades, conventional cancer therapies, including surgery, chemotherapy, and radiation, have remained the standard of care. While these treatments have significantly improved patient survival, they often affect healthy tissues and may not provide lasting benefits for patients with advanced or treatment-resistant cancers.

The 2026 laureates pioneered a different strategy: instead of directly attacking tumors, they developed methods to harness and strengthen the body's own immune system. Their collective work laid the scientific and clinical foundation for adoptive cell therapy, one of the most transformative advances in modern oncology [2,3].

### **Steven A. Rosenberg:** ***Unlocking the Potential of Tumor-Infiltrating Lymphocytes***

Dr. Steven A. Rosenberg, Chief of Surgery at the U.S. National Cancer Institute, pioneered the use of tumor-infiltrating lymphocytes (TILs).



IMAGE FROM TANG-PRIZE.ORG

During the 1980s, his research demonstrated that immune cells naturally present within tumors could be isolated, expanded in the laboratory, and reinfused into patients to mount a stronger anti-tumor response [3].

This approach produced durable clinical responses in patients with metastatic melanoma and provided the first compelling evidence that the immune system could be harnessed to eliminate established cancers. Rosenberg's pioneering work established many of the principles that continue to guide cellular immunotherapy today [3].



IMAGE FROM TANG-PRIZE.ORG

### **Michel Sadelain:** ***Engineering the Immune System***

Although naturally occurring immune cells can recognize some cancers, they are often unable to detect many tumor types effectively.

Dr. Michel Sadelain addressed this limitation by developing Chimeric Antigen Receptor (CAR) T-cell technology, which genetically engineers a patient's own T cells to recognize specific proteins expressed on cancer cells [2,4].

# Academic Highlight

## Advances in immunology

TANG-Prize 2026

His research transformed genetic engineering into a practical therapeutic strategy, demonstrating that modified T cells could selectively destroy cancer cells while minimizing damage to normal tissues. His discoveries paved the way for the development of several FDA-approved CAR-T therapies that are now used worldwide [4].

### Carl H. June: Translating CAR-T Therapy into Clinical Success

Dr. Carl H. June played a pivotal role in translating CAR-T cell technology from laboratory research to clinical practice. His landmark clinical trials demonstrated unprecedented success in patients with relapsed or treatment-resistant leukemia and lymphoma, many of whom had exhausted all available treatment options [2,5].



IMAGE FROM TANG-PRIZE.ORG

The remarkable clinical responses observed in these studies established CAR-T therapy as one of the most successful examples of personalized medicine. Today, CAR-T therapies are approved for several hematological malignancies and continue to expand into additional cancer types through ongoing clinical research [5].

### A Lasting Impact on Modern Medicine

Together, Rosenberg, Sadelain, and June transformed cancer immunotherapy from an experimental concept into a powerful clinical reality. Their discoveries have:

- Established adoptive cell therapy as a new pillar of cancer treatment.
- Enabled personalized therapies using patients' own immune cells.
- Inspired next-generation therapies targeting solid tumors.
- Accelerated advances in gene editing, synthetic biology, and regenerative medicine [2,4,5].

Beyond oncology, researchers are now exploring engineered immune cells for autoimmune diseases, infectious diseases, and regenerative medicine, highlighting the broad potential of cellular immunotherapy [4,5].

### Current Clinical Success and Therapeutic Efficacy of CAR-T Therapy

CAR-T cell therapy has progressed from an experimental strategy to an established treatment for several relapsed or refractory hematological malignancies. Clinical studies have demonstrated particularly high response rates in B-cell leukemias, lymphomas, and multiple myeloma. For example, FDA-reviewed data for lisocabtagene maraleucel in

relapsed/refractory marginal zone lymphoma showed an overall response rate of 84.4%, including a 55.8% complete response rate [6]. In multiple myeloma, BCMA-directed CAR-T therapies have similarly produced response rates exceeding 80% in some clinical settings [7]. Importantly, long-term follow-up indicates that a subset of patients can achieve remarkably durable remissions, with some remaining disease-free for many years after a single infusion [8]. These outcomes demonstrate the potential of CAR-T cells to provide durable, and in some patients potentially curative, responses in otherwise difficult-to-treat cancers.

### Looking Ahead

The 2026 Tang Prize recognizes more than three exceptional scientists; it celebrates a paradigm shift in medicine. By demonstrating that immune cells can be engineered into living medicines, Rosenberg, Sadelain, and June have reshaped the future of biomedical science [2].

As research continues to improve the safety, accessibility, and effectiveness of cellular therapies, their pioneering contributions will remain foundational to the next generation of precision medicine. The 2026 Tang Prize in Biopharmaceutical Science stands as a tribute to decades of scientific perseverance that have brought new hope to patients facing some of the world's most challenging cancers.

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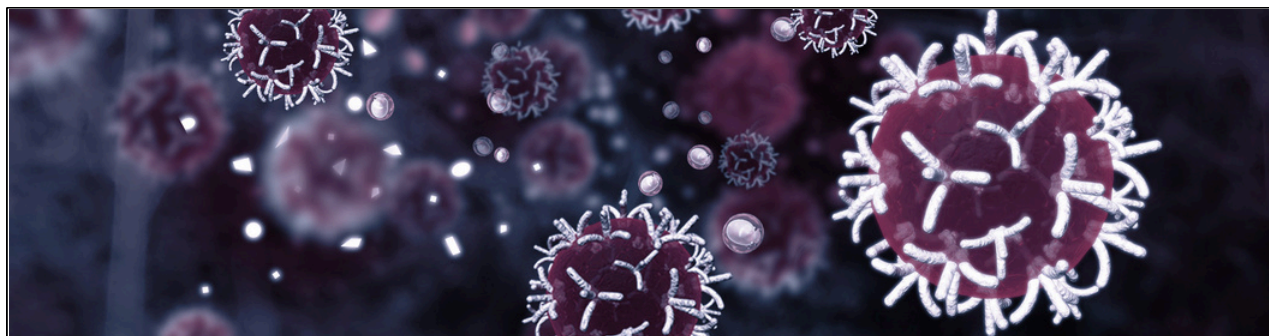


IMAGE FROM CANVA.COM

## T Cell-based Therapy: Milestones, Prospects and Market Perspective

### Innovations in T cell immunotherapy

T cell-based therapies have emerged as a transformative class of immunotherapeutic strategies in oncology, harnessing the cytotoxic potential of lymphocytes to selectively eliminate malignant cells. Among these, chimeric antigen receptor T cells (CAR-T) and bispecific T cell engagers (BiTEs) represent landmark advances, enabling either genetic reprogramming of patient-derived T cells or antibody-mediated redirection of endogenous T cells toward tumor antigens. While both approaches have demonstrated remarkable efficacy in hematologic malignancies, their application in solid tumors remains challenged by issues such as antigen heterogeneity, immunosuppressive microenvironments, and systemic toxicities including cytokine release syndrome.

To overcome these limitations, novel modalities such as bispecific antibody-armed T cells (Armed-T) are being developed, wherein functionally selected T cell subsets are expanded *ex vivo* and armed immediately prior to infusion. This strategy ensures the delivery of a large population of tumor-targeting effector cells with reduced risk of nonspecific activation, thereby offering a promising avenue for advancing T cell-based immunotherapy in solid cancers [1-5].

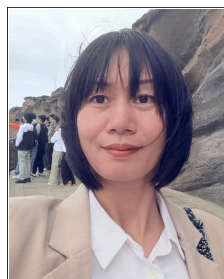
### Strengths and limitations of CAR-T, BiTEs, and Armed-T cells

CAR-T, BiTEs, and Armed-T cell therapies each present distinct strengths and limitations in cancer immunotherapy. CAR-T cells offer durable remissions in hematologic malignancies due to their long-term persistence, but they require complex, costly *ex vivo* engineering and carry risks of cytokine release syndrome and neurotoxicity, with limited efficacy in solid tumors.

BiTEs, by contrast, are off-the-shelf bispecific antibodies that provide immediate availability and scalable production, yet their short half-life necessitates continuous infusion and their efficacy is often less durable, relying heavily on the patient's endogenous T-cell fitness. Armed-T cells represent a hybrid approach, combining *ex vivo* expansion with antibody arming to enhance tumor targeting and reduce cytokine toxicity; however, they remain experimental, with moderate logistical complexity and uncertain long-term persistence. The features of these T cell-based therapies were detailed in Table 1[1-5].

### Outlook of T cell-based therapy

The outlook for T cell-based therapies in oncology is highly promising, with ongoing advances poised to expand their efficacy beyond hematologic malignancies into solid tumors. Continued refinement of chimeric antigen receptor T cells (CAR-T) and bispecific T cell engagers (BiTEs) is addressing challenges such as antigen heterogeneity, tumor microenvironment suppression, and systemic toxicities.



**Dr. Mai-Huong T. Ngo** is a researcher with extensive experience in sorafenib-resistant hepatocellular carcinoma. Her work has advanced the understanding of drug resistance mechanisms in liver cancer, and her recent research focuses on the application of armed-T cell therapy as a novel strategy for treating sorafenib-resistant HCC and other solid tumors.

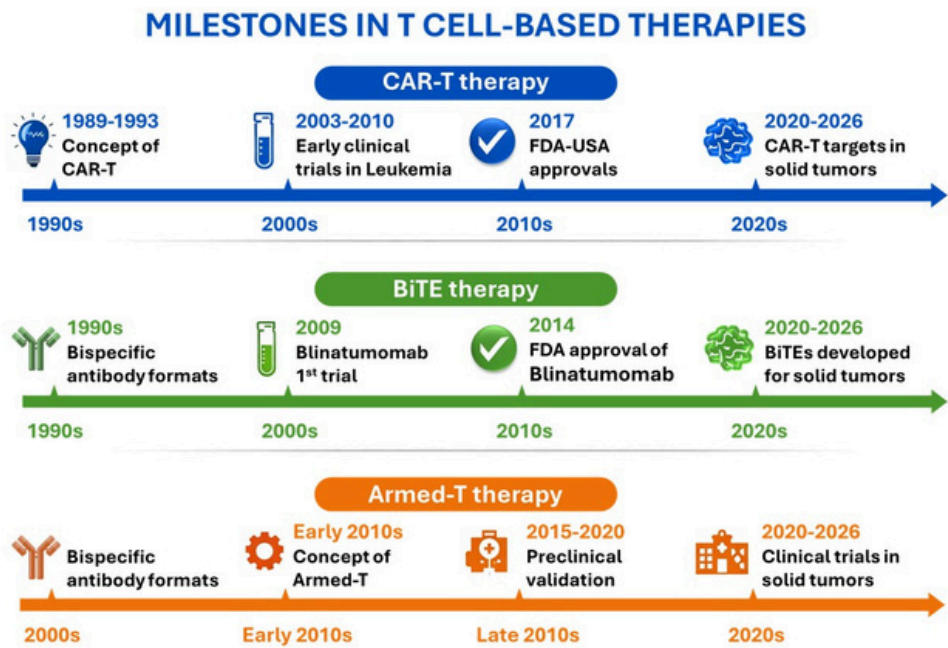


Figure 1. Strengths and limitations of CAR-T, BiTEs, and Armed-T cells

Emerging strategies, including bispecific antibody-armed T cells (Armed-T), armored CAR-T cells, and combination regimens with checkpoint inhibitors, are designed to enhance persistence, specificity, and safety. Moreover, innovations in gene editing, synthetic biology, and ex vivo expansion protocols are expected to generate more potent and durable effector populations. As these modalities progress toward clinical translation, T cell-based therapies are anticipated to become integral components of precision oncology, offering curative potential for previously intractable cancers [1-5].

Challenges of T cell-based therapy

Despite the encouraging outlook, T cell-based therapies continue to face significant challenges that limit their broader clinical application. A major obstacle is the immunosuppressive tumor microenvironment, which impairs T cell infiltration, persistence, and cytotoxic activity. Antigen heterogeneity and loss further contribute to therapeutic resistance, while systemic toxicities such as cytokine release syndrome (CRS) and neurotoxicity remain pressing safety concerns. Technical hurdles also persist, including the complexity and cost of ex vivo engineering for CAR-T cells, and the non-selective activation of T cell subsets by BiTEs, which can compromise efficacy and increase adverse effects. Moreover, manufacturing scalability, patient accessibility, and regulatory standardization present additional barriers to widespread adoption. Addressing these multifaceted challenges will be critical to realizing the full potential of T cell-based therapies in oncology [1-5].

Table 1. The advantages and disadvantages of CAR-T, BiTEs, and Armed-Tcell therapies

| Feature                | CAR-T Cells                                                                                                                    | BiTEs                                                                                                                    | Armed-T Cells                                                                                                                    |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Mechanism of Action    | Patient T cells are genetically engineered <i>ex vivo</i> to express chimeric antigen receptors that recognize tumor antigens. | Recombinant bispecific antibodies link CD3 on endogenous T cells to tumor antigens, redirecting T cells <i>in vivo</i> . | Functional T cells are selected and expanded <i>ex vivo</i> , then armed with bispecific antibodies immediately before infusion. |
| Manufacturing Process  | Complex, individualized cell engineering and expansion (weeks).                                                                | Off-the-shelf biologic drug; no cell manipulation.                                                                       | Moderate complexity - <i>ex vivo</i> expansion and antibody arming of selected T cells.                                          |
| Administration         | Single infusion of engineered cells.                                                                                           | Continuous or repeated infusion due to short half-life.                                                                  | Single or limited infusions of pre-armed effector T cells.                                                                       |
| Advantages             | Durable remission; long-term persistence; high efficacy in hematologic malignancies.                                           | Easy logistics; scalable; immediate availability.                                                                        | Controlled activation; reduced cytokine release; improved targeting in solid tumors.                                             |
| Limitations            | High cost; severe cytokine release syndrome (CRS); limited efficacy in solid tumors.                                           | Short half-life; non-selective activation of all CD3+ subsets; potential CRS.                                            | Requires <i>ex vivo</i> manipulation; still under clinical evaluation.                                                           |
| Representative Example | Tisagenlecleucel (Kymriah), Axicabtagene ciloleucel (Yescarta)                                                                 | Blinatumomab (CD19/CD3)                                                                                                  | Experimental platforms targeting EGFR, HER2, GPC3.                                                                               |
| Clinical Focus         | Hematologic malignancies (B-ALL, DLBCL).                                                                                       | Hematologic and emerging solid tumors.                                                                                   | Solid tumors with defined antigen targets.                                                                                       |

B-ALL: B-cell acute lymphoblastic leukemia  
CRS: severe cytokine release syndrome  
DLBCL: Diffuse large B-cell lymphoma

### Global market perspective

Parallel to scientific advances, the global market for T cell-based therapies is undergoing rapid expansion. CAR-T therapy is projected to grow from USD 10.92 billion in 2026 to USD 19.25 billion by 2034, at a Compound Annual Growth Rate (CAGR) of 7.34%, with North America maintaining a dominant share of over 70% and Asia-Pacific emerging as the fastest-growing region.

In contrast, the BiTEs market, though smaller in absolute value, is expanding at a much faster pace, expected to rise from USD 1.94 billion in 2026 to USD 4.18 billion by 2030 at a CAGR of 21.2%. This growth is driven by antibody engineering innovations, expansion into solid tumor indications, and strategic partnerships, exemplified by the FDA approval of Amgen's IMDELLTRA (tarlatamab-dlle) in 2024.

Together, these trends highlight a robust global trajectory in which CAR-T therapies dominate revenue while BiTEs reshape the immunotherapy landscape through accelerated adoption and diversification [6-11].

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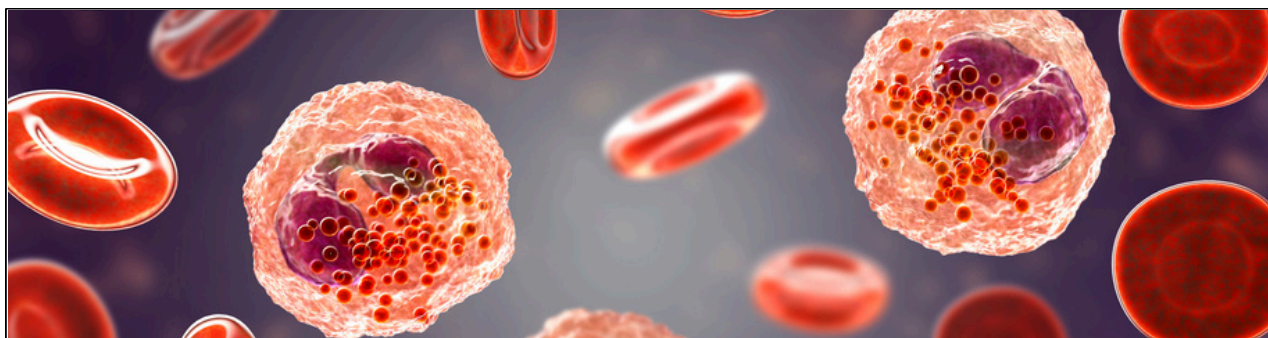


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## From First Responders to Tumor Accomplices: The Plasticity of Neutrophils in Cancer

### Abstract

Neutrophils are traditionally portrayed as short-lived innate immune cells that rapidly migrate to sites of infection or tissue injury. Cancer, however, can appropriate these emergency-response programs for its own benefit. Tumor-derived signals alter granulopoiesis, neutrophil maturation, trafficking, lifespan, and activation, generating heterogeneous neutrophil populations with markedly different functions. Some neutrophils retain antitumor activity through direct cytotoxicity, antibody-dependent killing, and support of adaptive immune responses. Others promote tumor growth by stimulating angiogenesis, remodeling the extracellular matrix, suppressing T-cell activity, escorting circulating tumor cells, establishing premetastatic niches, and releasing neutrophil extracellular traps. The historical N1-N2 polarization model provided an important framework for understanding this functional plasticity, but single-cell and spatial studies now reveal a continuum of maturation and activation states shaped by tumor type, anatomical location, disease stage, and treatment. Importantly, anticancer therapy may either reinforce suppressive neutrophil programs or generate interferon-responsive, tumor-controlling populations. This review traces the changing perception of neutrophils in cancer and discusses why selectively targeting harmful neutrophil programs may be more effective than indiscriminate neutrophil depletion.

**Keywords:** neutrophils; tumor microenvironment; tumor-associated neutrophils; neutrophil extracellular traps; metastasis; immunotherapy

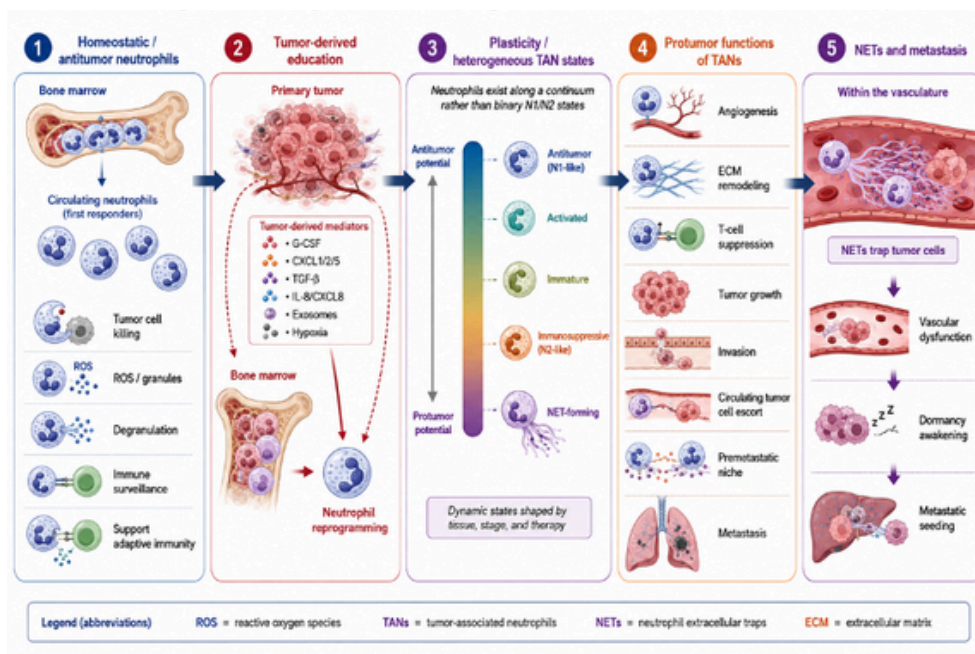
### The original script: arrive, attack, and repair

Neutrophils are the most abundant circulating leukocytes in humans and constitute one of the earliest cellular responses to infection and tissue damage. Guided by chemotactic signals, they rapidly exit the circulation and deploy antimicrobial mechanisms that include phagocytosis, reactive oxygen species, proteolytic granules, and neutrophil extracellular traps (NETs) [1]. These responses are powerful but potentially destructive; neutrophils must therefore be rapidly recruited, tightly regulated, and efficiently removed after completing their task.

Under physiological conditions, neutrophils contribute to immune surveillance through direct cytotoxicity, reactive oxygen species production, degranulation, and interactions with adaptive immune cells. In cancer, however, these protective functions may be progressively redirected toward tumor-supportive activities (Figure 1).

Cancer disrupts this normally transient response. A growing tumor resembles a wound that does not resolve, continuously producing inflammatory mediators, damage-associated signals, hypoxia, and necrotic material. These stimuli sustain neutrophil production and recruitment while exposing the cells to a microenvironment capable of changing their phenotype. Instead of merely entering tumors as terminally differentiated bystanders, neutrophils may be reprogrammed during development in the bone marrow, while circulating in the blood, and again after entering tumor tissues [2–6]. The major stages of this transition from homeostatic first responders to tumor-educated accomplices are summarized in Figure 1.

This recognition fundamentally changed the view of neutrophils in oncology. Tumor-associated neutrophils (TANs) are now understood as active components of the tumor ecosystem.



**Figure 1.** Neutrophils in cancer progression: from host defense to tumor support

Their contribution is not uniformly beneficial or harmful. Depending on context, neutrophils can destroy malignant cells, promote immune surveillance, or become potent facilitators of tumor progression (Figure 1).

### Beyond N1 and N2: neutrophils as changing cellular states

An influential early model divided TANs into antitumor “N1” and protumor “N2” phenotypes. In murine tumors, transforming growth factor- $\beta$  promoted an N2-like state, whereas its inhibition generated hypersegmented, inflammatory neutrophils with enhanced tumor-killing properties [2]. The model was conceptually valuable because it established that neutrophil behavior was plastic rather than predetermined.

Subsequent studies nevertheless showed that neutrophil biology cannot be fully represented by two stable categories. Differences in maturation, density, tissue location, metabolism, circadian age, and exposure to cytokines all influence neutrophil function [3–6]. Neutrophil phenotypes are therefore better understood as a functional continuum extending from cytotoxic and immunostimulatory states to immature, suppressive, NET-forming, and prometastatic states (Figure 2).

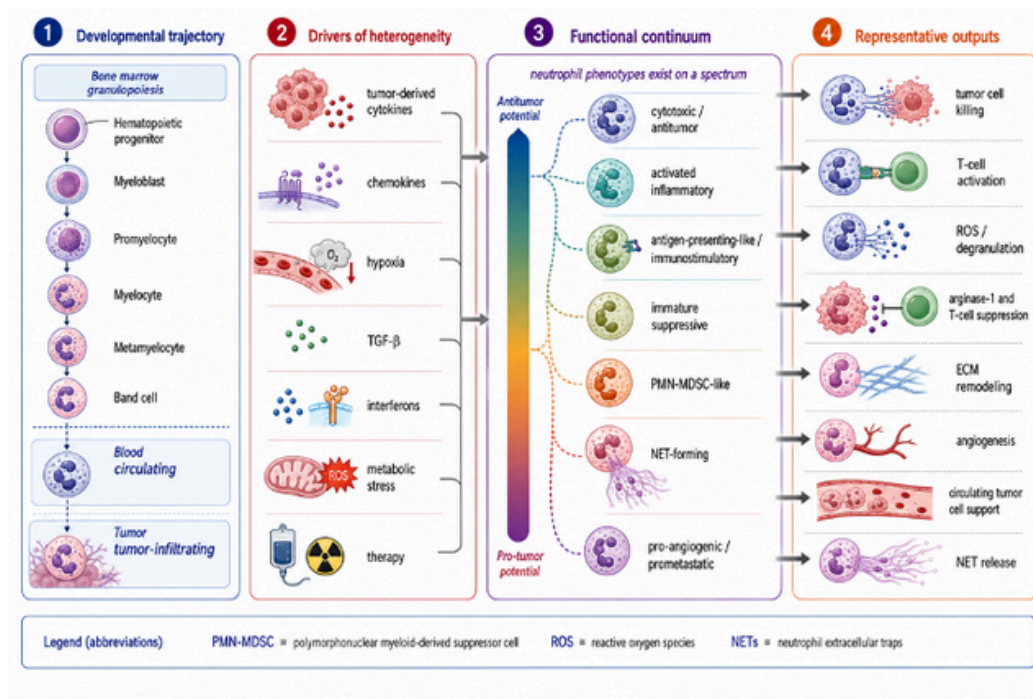
Low-density neutrophils, for example, include both immature immunosuppressive cells and activated mature cells, demonstrating that physical separation or a limited marker panel cannot reliably define biological function [3]. Considerable overlap also exists between immunosuppressive neutrophils and polymorphonuclear myeloid-derived suppressor cells.

In many settings, these terms describe intersecting functional states rather than completely distinct cellular lineages [4–6].

Neutrophil heterogeneity can arise at several points along their developmental trajectory. Tumor-derived cytokines and chemokines may alter granulopoiesis in the bone marrow, promote the premature release of immature neutrophils, and further modify mature neutrophils in the circulation or tumor microenvironment. Hypoxia, transforming growth factor- $\beta$ , interferons, metabolic stress, and anticancer therapy provide additional layers of regulation (Figure 2).

Single-cell RNA sequencing has provided a more detailed map of this heterogeneity. Analyses across human and murine lung cancers identified conserved neutrophil populations as well as species- and tissue-specific states [7]. In hepatocellular carcinoma, single-cell analysis revealed distinct trajectories from immature to mature neutrophils, including populations associated with poor prognosis and tumor-promoting interactions [8]. These findings suggest that neutrophils should be interpreted as a dynamic spectrum generated by developmental history and local instruction (Figure 2).

Spatial context is equally important. A neutrophil positioned in the circulation, at the invasive margin, within a hypoxic tumor core, or near metastatic vessels encounters different signals and cellular partners. Consequently, the same marker may not indicate the same function across compartments.



**Figure 2.** Neutrophils heterogeneity and functional states in cancer

This complexity helps explain why high neutrophil abundance or an elevated blood neutrophil-to-lymphocyte ratio is frequently associated with unfavorable outcomes but cannot, by itself, establish what the neutrophils are doing [9].

### How tumors recruit and corrupt first responders

Tumors influence neutrophils before the cells reach the primary lesion. Cancer-derived granulocyte colony-stimulating factor, CXCL-family chemokines, inflammatory cytokines, metabolites, and extracellular vesicles can stimulate emergency granulopoiesis and release immature neutrophils into the circulation [4–6]. Once recruited through pathways such as CXCL1/2/5–CXCR2, neutrophils are exposed to hypoxia, transforming growth factor- $\beta$ , interleukins, lipid mediators, and tumor-derived extracellular vesicles. These interconnected mechanisms of neutrophil recruitment and reprogramming are illustrated in Figure 1.

Nevertheless, antitumor neutrophil activity remains biologically possible. In experimental models, neutrophils recruited to the lung before metastatic colonization directly eliminated disseminated tumor cells through hydrogen peroxide-dependent mechanisms [10]. Neutrophils can also inhibit tumor growth by releasing the receptor tyrosine kinase MET in response to tumor-derived signals, illustrating how pathways commonly associated with cancer cells may produce opposite effects in immune cells [11]. Additional antitumor mechanisms include antibody-dependent cellular cytotoxicity, production of inflammatory cytokines, recruitment of lymphocytes, and interactions that support T-cell activation (Figures 1 and 2).

The balance often shifts as tumors progress. Tumor-conditioned neutrophils release vascular endothelial growth factor, matrix metalloproteinases, elastase, and other granule components that promote angiogenesis, extracellular-matrix degradation, invasion, and growth-factor availability. They may suppress T-cell responses through arginase-1, reactive oxygen species, nitric oxide-related pathways, checkpoint ligands, and competition for essential metabolites [4–6]. The principal protumor outputs of TANs, including angiogenesis, extracellular-matrix remodeling, T-cell suppression, tumor-cell invasion, and metastatic support, are summarized in Figures 1 and 2.

In breast cancer models, interleukin-17-producing  $\gamma\delta$  T cells induced systemic neutrophil expansion, and these neutrophils suppressed cytotoxic CD8-positive T cells, thereby facilitating metastasis [12]. Cancer therefore does not necessarily create a completely new neutrophil program. Rather, it redirects normal emergency functions. Proteases intended to clear damaged tissue can open invasion paths. Oxidants designed to kill microorganisms can suppress lymphocytes or damage surrounding tissue. Proangiogenic and repair signals intended to restore perfusion can feed a growing tumor. Mechanisms that are protective during acute injury become harmful when activated continuously (Figure 1).

### Accomplices in the metastatic event

Neutrophils can assist cancer cells at nearly every stage of metastasis. At the primary tumor, they promote invasion and vascular entry. In the circulation, they form heterotypic clusters with circulating tumor cells.



Analysis of patients with breast cancer showed that neutrophil-associated circulating tumor cells had enhanced proliferative activity and a greater capacity to generate metastases than isolated tumor cells [13]. Thus, neutrophils may operate not only as passive shields but also as cellular escorts that provide survival and growth signals (Figure 1).

Distant organs may also be conditioned before tumor cells arrive. Tumor-derived signals recruit neutrophils to future metastatic sites, where they remodel extracellular matrix, alter vascular permeability, and create inflammatory niches. In breast cancer models, neutrophils accumulated in the premetastatic lung and promoted colonization through leukotriene production, selectively supporting highly tumorigenic cancer-cell subclones [14].

NET formation is one of the clearest examples of an antimicrobial mechanism being repurposed by cancer. NETs consist of decondensed chromatin decorated with histones, elastase, myeloperoxidase, and other granule proteins [15]. They were originally characterized as structures that immobilize microorganisms, but cancer-associated NETs can capture circulating tumor cells, facilitate adhesion to vascular or tissue surfaces, and promote metastatic seeding [16]. NET-associated proteases can also remodel extracellular matrix proteins and awaken dormant cancer cells, providing a potential link between inflammation and late metastatic relapse [17].

NETs additionally connect cancer with thrombosis and vascular dysfunction. Tumor-bearing mice develop systemic neutrophil priming and increased NET formation, which can contribute to cancer-associated hypercoagulability [15]. More recently, neutrophils and NETs were shown to obstruct tumor-associated blood vessels, generating necrosis while paradoxically increasing metastatic dissemination [23]. These findings reveal a counterintuitive process: neutrophil-mediated vascular damage may destroy parts of a tumor yet simultaneously select for aggressive cells and create routes for escape. The proposed sequence linking NET-mediated tumor-cell trapping, vascular dysfunction, dormancy awakening, and metastatic seeding is shown in Figure 1.

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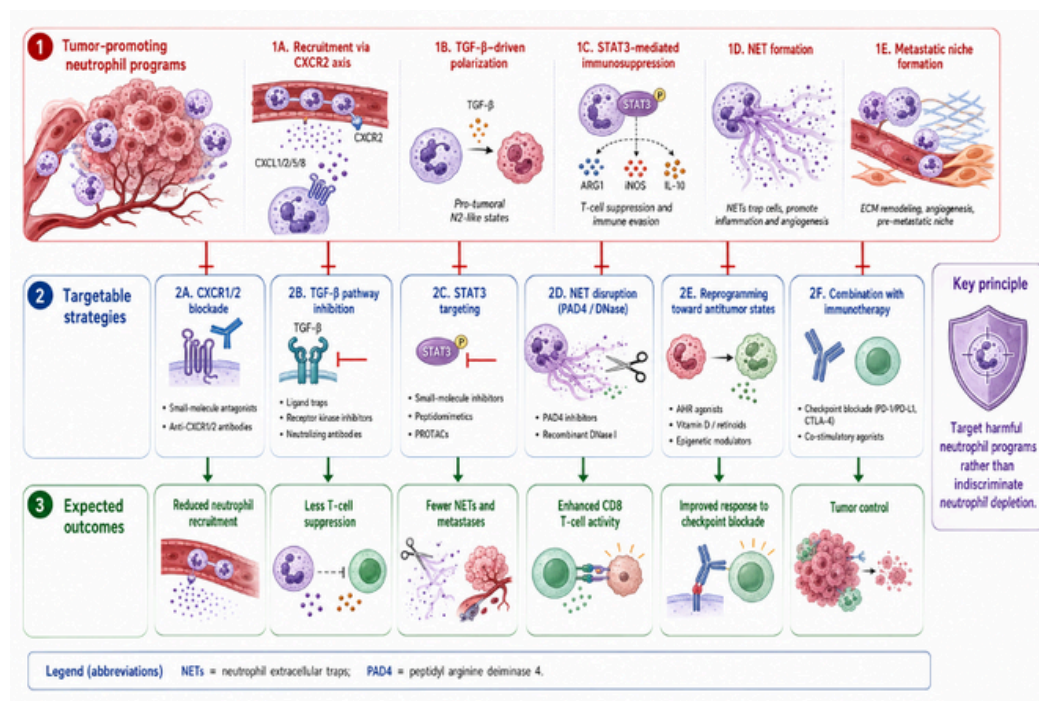
#### **Treatment as a second rewiring event**

Anticancer treatment does not merely eliminate tumor cells; it changes the inflammatory environment in which neutrophils develop and function. Chemotherapy-induced cell death can release damage-associated molecules and cytokines that recruit or activate neutrophils. In some tumors, this response contributes to resistance. Chemotherapy was shown to induce NET formation and activate latent transforming growth factor- $\beta$ , creating an immunosuppressive environment that reduced treatment efficacy [19].

The relationship is not universal. In a colorectal cancer model, chemotherapy-induced NETs inhibited tumor growth rather than promoting it [20]. Although apparently contradictory, these observations reinforce the central principle that neutrophil functions are context-dependent. Tumor origin, microbial exposure, treatment type, NET composition, timing, and the surrounding immune landscape may determine whether the resulting response supports tumor control or recovery.

Immunotherapy provides further evidence that neutrophils can be therapeutically redirected. In preclinical cancer models, successful immunotherapy induced an interferon-stimulated neutrophil state with enhanced antitumor activity [21]. A related study identified IRF1-dependent neutrophils that were required for effective immunotherapy and associated with favorable responses in patients [22]. These observations support therapeutic strategies that reprogram neutrophils toward antitumor states rather than eliminating the entire neutrophil population (Figure 3).

Neutrophils may consequently serve as both mediators and biomarkers of treatment response. A high circulating neutrophil count is often interpreted as evidence of suppression, yet numerical abundance does not reveal cellular state. Interferon-responsive mature neutrophils, immature suppressive neutrophils, senescent cells, and NET-forming neutrophils could have opposite effects despite contributing to the same total count. Biomarker strategies will therefore need to combine abundance with maturation, transcriptional state, activation, tissue localization, and functional assays.



**Figure 3.** Therapeutic targeting of neutrophil programs in cancer

### Target the program as the main strategy

The therapeutic appeal of neutrophils is accompanied by an obvious risk. Global neutrophil depletion would compromise antimicrobial defense and tissue repair. A more rational objective is to interrupt the specific pathways through which tumors recruit, educate, or exploit neutrophils.

Potential approaches include CXCR1/2 blockade to restrict tumor-directed neutrophil recruitment, inhibition of transforming growth factor- $\beta$  or STAT3-dependent suppressive programs, disruption of NET formation using PAD4 inhibitors or DNase-based strategies, and reprogramming of neutrophils toward antitumor phenotypes [5,6,18]. These strategies and their expected effects on T-cell activity, NET formation, metastasis, and checkpoint immunotherapy are summarized in Figure 3.

Recent neutrophil-specific STAT3 targeting reduced tumor progression and expanded cytotoxic CD8-positive T-cell responses, supporting the feasibility of selectively disabling suppressive neutrophil programs [24]. Other strategies may seek to enhance Fc receptor-mediated cytotoxicity or preserve interferon-responsive neutrophils during immunotherapy. Combining neutrophil-directed interventions with immune-checkpoint blockade may therefore improve antitumor immunity while avoiding the infectious risks associated with indiscriminate neutrophil depletion (Figure 3). Translation will require more precise definitions. Many mechanistic studies rely on mouse models, whereas human neutrophils differ in marker expression, lifespan, and sensitivity to experimental manipulation.

Sample processing can itself activate neutrophils or induce changes in density, transcription, and NET formation. Prospective human studies should therefore integrate blood and tissue analysis, spatial imaging, single-cell or proteomic profiling, and longitudinal sampling before and after treatment [5,6,25].

### Conclusion

The story of neutrophils in cancer has evolved from one of simple recruitment to one of profound cellular adaptation. These cells are neither inherently tumor-promoting nor reliably antitumor. They are rapid-response effectors whose normal functions killing, proteolysis, vascular modification, immune regulation, and tissue repair can be redirected by malignant tissues.

The N1-N2 framework first captured this plasticity, but current evidence supports a multidimensional continuum shaped by maturation, anatomy, tumor stage, systemic inflammation, and therapy. Neutrophils may kill disseminated cells in one setting, suppress lymphocytes in another, and change function again following chemotherapy or immunotherapy. NETs similarly illustrate how the same biological mechanism can promote thrombosis, dormancy escape, treatment resistance, or, under selected conditions, tumor control.

The central therapeutic challenge is therefore not to remove neutrophils indiscriminately. It is to identify when, where, and how they become tumor accomplices and to selectively disarm those programs while preserving or restoring their capacity to defend the host.

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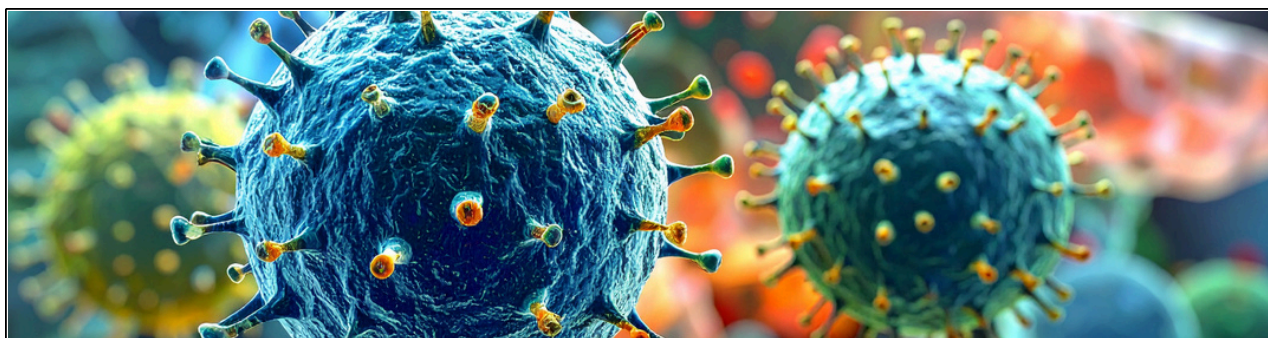


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## CD19 and BCMA CAR-T Cell Therapy: A New Era in Autoimmune Disease Treatment

### Introduction

Autoimmune disorders arise when immune tolerance breaks down, leading the immune system to mistakenly recognize self-tissues as foreign. These conditions collectively affect roughly 5–10% of individuals worldwide and include diseases such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, multiple sclerosis, and inflammatory myopathies. Standard management typically involves corticosteroids, biologic agents, and other immunosuppressive drugs aimed at controlling inflammation and limiting tissue injury. While these approaches can reduce disease activity, they rarely eradicate the autoreactive immune populations that drive pathology, which allows disease flares and cumulative organ damage to persist over time (1,2).

In recent years, cellular immunotherapy has introduced a fundamentally different therapeutic concept. Chimeric antigen receptor T-cell (CAR-T) therapy, initially developed for hematologic malignancies, is now being explored as a treatment option for severe and refractory autoimmune diseases (2–4). Rather than broadly suppressing immune function, this strategy selectively eliminates disease-driving B-cell populations responsible for autoantibody production. Among the most studied targets are CD19 and B-cell maturation antigen (BCMA), which are expressed at distinct stages of B-cell differentiation.

### Role of B Cells in Autoimmune Pathogenesis

B lymphocytes normally play a protective role in adaptive immunity by generating antibodies against pathogens. However, in autoimmune conditions, a subset of these cells becomes dysregulated and produces antibodies that target self-antigens. These autoantibodies contribute to chronic inflammation through immune complex deposition, complement activation, and recruitment of inflammatory mediators, ultimately resulting in tissue injury (2,6).

Conventional B-cell depletion strategies such as rituximab primarily eliminate CD20-positive mature B cells. Despite their effectiveness, these therapies do not fully eradicate early B-cell precursors or long-lived plasma cells, allowing autoantibody production to persist and disease relapse to occur after immune reconstitution (2,6). CAR-T therapy has therefore been proposed as a more durable strategy capable of sustained elimination of pathogenic B-cell subsets and long-term immune reprogramming (3,7).

### CD19-Directed CAR-T Therapy

CD19 is broadly expressed across most stages of B-cell development, including early precursors, naïve cells, and memory B cells, but is not present on fully differentiated plasma cells (2,3). The production of CD19 CAR-T cells involves harvesting patient T cells, genetically engineering them to express a CD19-specific receptor, expanding them *ex vivo*, and reinfusing them after lymphodepleting conditioning (7).

Once administered, these modified T cells recognize CD19-positive cells and eliminate them through cytotoxic mechanisms involving perforin release, granzymes, and cytokine-mediated effects. Unlike antibody-based therapies, CAR-T cells can expand *in vivo* and persist for extended periods, enabling continuous surveillance and removal of newly emerging autoreactive B cells (3,7).

Clinical experience has shown promising outcomes in patients with refractory autoimmune diseases. In severe systemic lupus erythematosus, a single infusion has been associated with rapid remission, reduction of autoantibody titers, restoration of immune balance, and discontinuation of immunosuppressive therapy (1,2).

Similar therapeutic responses have been reported in systemic sclerosis, inflammatory myopathies, vasculitis, and anti-synthetase syndrome, supporting the concept that CD19 CAR-T therapy may induce a long-lasting immune reconfiguration rather than temporary suppression (2,3).

### BCMA-Targeted CAR-T Therapy

Although CD19-directed therapy effectively depletes most B-cell populations, it has limited impact on long-lived plasma cells, which typically lose CD19 expression but retain BCMA expression (2,6). These plasma cells are a major source of persistent autoantibody production and therefore represent a critical therapeutic target.

BCMA serves as a key survival receptor for plasma cells, interacting with BAFF and APRIL signaling pathways to support their longevity (6). CAR-T cells engineered to target BCMA can selectively eliminate these antibody-secreting cells, thereby reducing chronic autoantibody levels and potentially improving long-term disease control (3,6).

The established efficacy of BCMA CAR-T therapy in multiple myeloma has encouraged its investigation in autoimmune diseases (5). Ongoing studies are evaluating its role in conditions such as lupus nephritis, myasthenia gravis, and autoimmune neurological disorders. Early clinical data suggest meaningful reductions in pathogenic antibodies and sustained clinical improvement in selected patients (3,6).

### Combined CD19/BCMA CAR-T Strategy

Because CD19 and BCMA are expressed on different stages of B-cell maturation, simultaneous targeting of both antigens may provide a more complete depletion of autoreactive immune cells than single-target approaches (3).

This dual-target strategy aims to eliminate:

- Immature and mature autoreactive B cells via CD19 targeting
- Memory B-cell populations expressing CD19
- Long-lived plasma cells expressing BCMA

By addressing both precursor and antibody-secreting compartments, this approach may enhance immune system rebalancing and reduce the likelihood of relapse. Early clinical findings are encouraging, showing acceptable safety and promising efficacy, although larger controlled trials are still required to confirm long-term outcomes (2,3,8).

### Limitations and Challenges

Despite its therapeutic potential, CAR-T therapy faces several important limitations. Each treatment is patient-specific, requiring individualized manufacturing from autologous T cells, which increases cost and production time.

Additionally, patients must undergo lymphodepleting chemotherapy and require close clinical monitoring after infusion (3,7).

The most frequently observed toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Notably, patients with autoimmune diseases often experience less severe CRS compared to oncology patients, likely due to a lower overall burden of target cells (2,3).

Prolonged depletion of B cells may also increase infection risk and, in some cases, necessitate immunoglobulin replacement therapy (3). To overcome these challenges, next-generation approaches are being developed, including fully human CAR constructs, allogeneic “off-the-shelf” CAR-T products, and CAR-engineered natural killer (CAR-NK) cells, all of which aim to improve safety, scalability, and accessibility (3,7).

### Future Outlook

The emergence of CD19- and BCMA-directed CAR-T therapies represents a major shift in autoimmune disease management. Instead of continuous immunosuppression, these therapies aim to remove the underlying cellular drivers of disease and allow immune system reconstitution with restored tolerance (2,3).

Although further randomized clinical trials are necessary to confirm durability and safety, early clinical evidence suggests that CAR-T therapy may enable long-term, treatment-free remission in patients with severe, refractory autoimmune diseases (1–3). As manufacturing processes improve and costs decrease, CAR-T-based strategies are expected to become an increasingly important component of precision medicine for autoimmune disorders.

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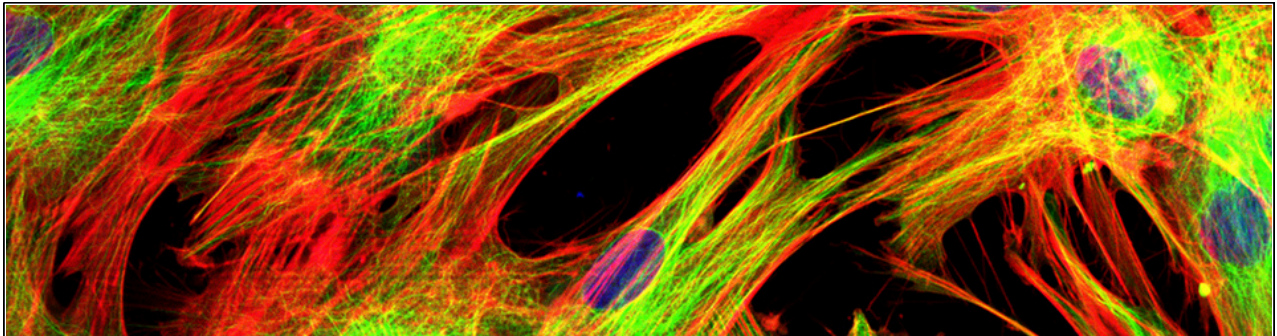


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## ELIXCYTE<sup>®</sup> (Allogeneic Mesenchymal Stem Cell): An Integrated Translational Framework Supporting Clinical Development, Mechanism of Action, and Potency Assessment

### Abstract

Osteoarthritis (OA) and chronic kidney disease (CKD) are major chronic degenerative diseases representing significant unmet medical needs. Developed by UnicoCell Biomed, ELIXCYTE<sup>®</sup> is an allogeneic adipose-derived stem cell (ADSC) product currently in advanced clinical development, having completed Phase III enrollment for OA and Phase I/II trial for CKD. To support clinical development and regulatory approval, comprehensive studies were conducted to investigate the mechanism of action (MOA) and potency of ELIXCYTE<sup>®</sup>. Across both disease settings, ELIXCYTE<sup>®</sup> demonstrated consistent immunomodulatory activity through IDO-mediated immune regulation, modulation of inflammatory macrophage responses, and secretion of anti-inflammatory factors. In OA models, it preserved cartilage homeostasis by reducing catabolic activity and maintaining extracellular matrix integrity. In CKD models, ELIXCYTE<sup>®</sup> exhibited anti-fibrotic and pro-angiogenic activities through regulation of fibrosis-associated pathways and preservation of the renal microenvironment. Together, these findings establish a scientific framework linking MOA, potency, and clinical development, highlighting the potential of ELIXCYTE<sup>®</sup> as a standardized allogeneic cell therapy product for multiple chronic degenerative diseases.

**Keywords:** ELIXCYTE<sup>®</sup>, adipose-derived stem cells (ADSCs), osteoarthritis, chronic kidney disease, immunomodulation, potency assay, regenerative medicine

<sup>#</sup>These authors contributed equally to this work

\*Corresponding author: Yi-Pei Hung

e-mail: Yipeihung@unicocell.com



UnicoCell Biomed is a biotechnology company focused on developing allogeneic, "off-the-shelf" cellular biologics for degenerative diseases.

ELIXCYTE<sup>®</sup> cell therapy platform across multiple late-stage product candidates:

- ELIXCYTE<sup>®</sup>-OA for knee osteoarthritis which has successfully completed its Phase III clinical trial enrollment.
- ELIXCYTE<sup>®</sup>-CKD for chronic kidney disease, which has completed Phase I/II clinical trials with favorable safety profile and encouraging efficacy outcome.

**ELIXCYTE<sup>®</sup>** is resourced from healthy donor and expanded through a proprietary process. Through UnicoCell's robustness manufacturing process allowing for scale-up production and guaranteeing exceptional batch-to-batch consistency with the evidence from accumulating long-term stability. To compliance with global acceptance of biologics and the strict safety benchmarks, UnicoCell followed ICH quality requirements and FDA industry guideline, and then built up the cell bank systems with the Master File (MF) acknowledgment from FDA. Furthermore, UnicoCell has past the inspections of PIC/S GMP pilot plant by TFDA and Cell Processing Center by Japan PMDA. Also, UnicoCell has established multiple platforms in potency assessments and MOA to rigorously validate the multi-targeted biological activities. ELIXCYTE<sup>®</sup> demonstrating a promising "multiple-indications medication" via the successfully targets shared pathological hallmarks across completely different organ systems. These platforms versatility holds the potential to address substantial and urgent unmet medical needs, bringing a transformative therapeutic option to patients suffering from irreversible degenerative diseases.

## Introduction

Chronic degenerative diseases and progressive organ failure impose an immense and escalating global burden, presenting critical unmet medical needs that conventional pharmaceuticals often fail to adequately address. Osteoarthritis (OA) and chronic kidney disease (CKD) are among the most prevalent chronic degenerative disorders and share common pathological hallmarks, including persistent inflammation, progressive tissue deterioration, and functional irreversible functional decline<sup>[1-3]</sup>. While current standard-of-care treatments primarily focus on symptom management or delaying late-stage interventions such as joint replacement and dialysis, they generally do not restore damaged tissue architecture or fundamentally alter disease progression.

To address these challenges, allogeneic mesenchymal stem cell (MSC) therapy has emerged as promising regenerative approaches, leveraging their immunomodulatory, paracrine, and tissue-supportive properties to target key drivers of chronic degeneration<sup>[4, 5]</sup>. Among these, ELIXCYTE®, an ADSC-based cell therapy developed by UnicoCell Biomed, has advanced into late-stage clinical development for both OA and CKD, representing a clinically validated regenerative medicine strategy for chronic degenerative diseases.

ELIXCYTE® is an off-the-shelf allogeneic ADSC-based cell therapy product to provide a scalable and standardized regenerative medicine solution for chronic degenerative diseases. Supported by a robust master and working cell banking system and PIC/S GMP-compliant manufacturing infrastructure, it has established a strong foundation for global clinical development and commercialization. Notably, its manufacturing platform has successfully obtained a DMF from the FDA that reflects the company's commitment to manufacturing quality, regulatory readiness, and product consistency.

Building upon this foundation, ELIXCYTE® has advanced into late-stage clinical development across multiple indications. In OA, the program achieved a major milestone with the successful completion of enrollment in a randomized, double-blind Phase III clinical trial. In parallel, the CKD program has completed Phase I/II clinical studies, demonstrating a favorable safety profile and encouraging clinical outcomes. Together, these achievements position ELIXCYTE® among a limited number of allogeneic stem cell products that have progressed into advanced clinical development while advancing toward market readiness.

While these clinical achievements represent important milestones, the successful development and commercialization of advanced cell therapies also require a clear understanding of their underlying biological mechanisms and functional potency. For cell-based products, establishing a scientifically supported MOA together with quantitative potency assessment strategies is essential for ensuring product consistency, demonstrating biological activity, and meeting evolving global regulatory expectations<sup>[6, 7]</sup>.

Recognizing this need, UnicoCell has invested extensively in research aimed at understanding the biological mechanisms underlying ELIXCYTE®'s therapeutic effects and translating those insights into measurable potency attributes. Through integrated investigations spanning immunomodulation, cartilage protection, and renal protection, the company has established a science-driven framework linking biological activity, product quality, and clinical performance.

In the following sections, we summarize the clinical, mechanistic, and potency-related findings that support the development of ELIXCYTE®. Together, these studies illustrate how the integration of clinical validation, mechanistic understanding, and regulatory-oriented potency assessment can establish a robust scientific foundation for next-generation regenerative medicine products.

## Core therapeutic mechanism of OA and CKD Disease modification

The International Society for Cell & Gene Therapy (ISCT) recognizes immunomodulatory activity as a critical determinant of MSC therapeutic function, with indoleamine 2,3-dioxygenase (IDO) serving as one of the most widely accepted functional markers of MSC potency<sup>[7]</sup>. Given that chronic inflammation and immune dysregulation are central pathological features shared by both OA and CKD, UnicoCell established a robust immunomodulatory potency platform to characterize the biological activity of ELIXCYTE® across disease indications.

Upon stimulation with interferon-gamma (IFN- $\gamma$ ), ELIXCYTE® consistently upregulates IDO expression, resulting in potent suppression of T-cell proliferation. This immunomodulatory activity was reproducibly observed across multiple manufacturing batches, supporting the robustness and consistency of the ELIXCYTE® potency framework<sup>[8]</sup>.

In addition to regulating adaptive immune responses, ELIXCYTE® also modulates innate inflammatory pathways. Using an inflammatory macrophage coculture system, it significantly reduced the proportion of M1-polarized macrophages, demonstrating a reproducible anti-inflammatory effect<sup>[9]</sup>. Although the precise mechanisms underlying this observation remain under investigation, previous studies have suggested that reductions in M1 macrophages may result from inhibition of M0-to-M1 polarization, phenotypic transition of inflammatory macrophages toward anti-inflammatory states, or a combination of both mechanisms. Further mechanistic studies are ongoing to better define the contribution of these pathways to ELIXCYTE®-mediated immunomodulation.



Paracrine signaling also appears to play an important role in this process. Among the secreted factors produced by ELIXCYTE®, hepatocyte growth factor (HGF) and prostaglandin E2 (PGE2) were consistently detected across multiple manufacturing batches and have been widely reported to contribute to MSC-mediated immunoregulation and suppression of inflammatory macrophage activation<sup>[8,13,14]</sup>. Consistent with these observations, ELIXCYTE® treatment was associated with increased levels of anti-inflammatory mediators, including IL-1RA and IL-10, together with reduced levels of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in disease-relevant experimental models<sup>[9]</sup>. These changes suggest that ELIXCYTE® may actively shift the immune microenvironment from a pro-inflammatory to tissue repair, thereby attenuating sustained immune activation and promoting tissue homeostasis.

Collectively, these findings support a unified immunomodulatory framework through which ELIXCYTE® regulates both adaptive and innate immune responses. The reproducibility of IDO activity, T-cell suppression, macrophage modulation, and anti-inflammatory paracrine signaling across manufacturing batches further supports the development of mechanism-driven potency assays that may serve as important indicators of product quality and biological activity.

#### **Cartilage Protection and Articular Microenvironmental Regulation in OA**

OA is characterized by a progressive imbalance between catabolic and anabolic activities within the joint microenvironment, leading to chronic inflammation, cartilage degradation, and functional deterioration<sup>[1]</sup>. Therefore, effective disease-modifying strategies must not only suppress inflammatory and degradative pathways but also preserve the viability and functional integrity of resident chondrocytes. Consistent with current concepts in regenerative medicine and cartilage biology, ELIXCYTE® was evaluated for its ability to regulate the OA microenvironment and protect cartilage from progressive degeneration.

Using both inflammatory osteoarthritis coculture systems and ex vivo osteoarthritis synovial fluid (OA-SF) models, ELIXCYTE® demonstrated potent chondroprotective activity under disease-relevant conditions. In the OA-SF model, synovial fluid collected from OA patients induced a degenerative microenvironment that promoted cartilage catabolism. The addition of ELIXCYTE® effectively reduced the expression of cartilage degradation-associated proteins while simultaneously promoting the secretion of anti-inflammatory mediators and suppressing pro-inflammatory cytokines<sup>[9]</sup>. Consistent with these observations, exposure to ELIXCYTE® significantly reduced the expression of matrix metalloproteinase-13 (MMP13), a key enzyme implicated in cartilage matrix degradation<sup>[9]</sup>.

At the same time, expression of cartilage-associated matrix components, including collagen type II alpha 1 (COL2A1) and aggrecan (ACAN), was preserved or enhanced, indicating maintenance of extracellular matrix homeostasis despite ongoing inflammatory stimulation.

Among the bioactive factors secreted by ELIXCYTE®, platelet-derived growth factor-BB (PDGF-BB) was consistently detected and associated with preservation of chondrocyte proliferative capacity under inflammatory conditions<sup>[9]</sup>. These findings suggest that ELIXCYTE® not only modulates the pathological OA microenvironment but may also support the maintenance of cellular functions required for cartilage integrity.

The cartilage-protective activity observed in vitro was further supported by multiple preclinical OA models, including Monosodium Iodoacetate-induced osteoarthritis (MIA) rat, Anterior Cruciate Ligament Transection (ACLT) rabbit, Medial Meniscal Transection (MMT) swine, and spontaneous STR/ort models<sup>[10, 11]</sup>. Across these studies, ELIXCYTE® consistently demonstrated reductions in inflammatory and degenerative changes together with preservation of joint structure and cartilage integrity. Collectively, these findings support a mechanism through which ELIXCYTE® regulates the articular microenvironment, suppresses catabolic pathways, and preserves cartilage homeostasis, providing a scientific rationale for its ongoing late-stage clinical development in OA.

#### **Prevention of Chronic kidney disease progression**

Progressive CKD is characterized by persistent inflammation, excessive extracellular matrix accumulation, microvascular rarefaction, and progressive loss of renal function<sup>[2]</sup>. Among these pathological features, tubulointerstitial fibrosis is widely recognized as a major determinant of CKD progression toward end-stage renal disease<sup>[2]</sup>.

To investigate the renal-protective activity of ELIXCYTE®, a series of complementary in vitro and in vivo models were established, including inflammatory coculture systems, unilateral ureteral obstruction (UUO), adenine-induced nephropathy, and 5/6 nephrectomy models. Across these disease-relevant platforms, ELIXCYTE® consistently demonstrated anti-fibrotic and tissue-protective activities, supporting its potential application in progressive CKD<sup>[8]</sup>.

Mechanistically, ELIXCYTE® treatment was associated with suppression of transforming growth factor-beta (TGF- $\beta$ )-related fibrotic signaling and reduced accumulation of key extracellular matrix components, including fibronectin and collagen I. These findings suggest that it may attenuate pathological fibrotic remodeling and contribute to preservation of renal tissue architecture under chronic injury conditions<sup>[8]</sup>.

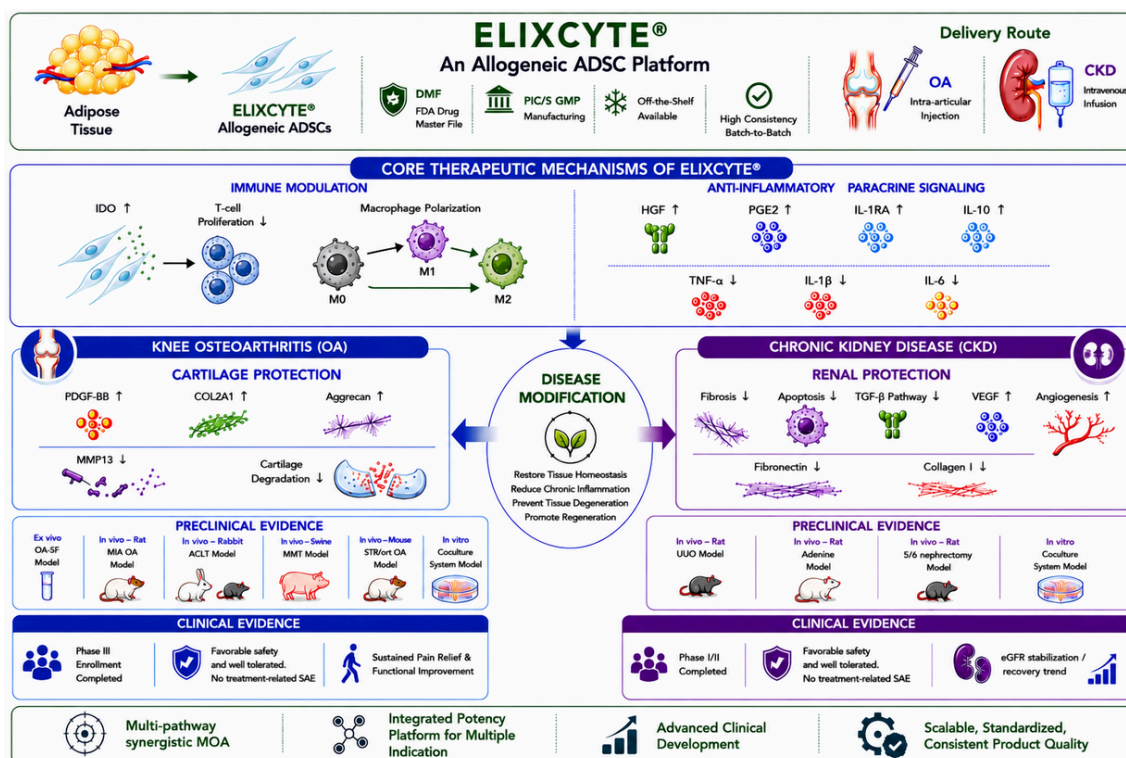


Figure 1. ELIXCYTE®: A Multi-Mechanistic Platform for Disease Modification in OA and CKD

In addition to its anti-fibrotic activity, ELIXCYTE® demonstrated pro-angiogenic potential through its secretion of vascular endothelial growth factor (VEGF) and other bioactive paracrine factors. Consistent with these observations, enhanced angiogenic activity and improved endothelial cell function were observed in experimental models, supporting its role in maintaining microvascular integrity within the injured kidney<sup>[8]</sup>. Furthermore, emerging evidence suggests that preservation of the renal microenvironment through anti-fibrotic and pro-angiogenic mechanisms may also contribute to protection against cellular injury and apoptosis, although the precise contribution of apoptosis-related pathways remains under investigation.

Collectively, these findings support a dual mechanism through which ELIXCYTE® simultaneously mitigates fibrotic progression and promotes microvascular repair. The consistency of these observations across multiple CKD models provides a strong biological rationale for the favorable safety profile and encouraging clinical outcomes observed in completed Phase I/II studies and further supporting the continued clinical development of ELIXCYTE® for CKD.

#### Clinical Translation of ELIXCYTE® in OA and CKD

In OA, ELIXCYTE® has successfully advanced into a randomized, double-blind Phase III clinical trial, with enrollment completed. Clinical observations demonstrated a favorable safety profile, no treatment-related serious adverse events (SAEs), and sustained therapeutic benefits up to one year following a single intra-articular administration, with effects maintained through 96 weeks of follow-up<sup>[12]</sup>.

In parallel, ELIXCYTE® has completed Phase I/II clinical studies in CKD, demonstrating a favorable safety and tolerability profile with no treatment-related serious adverse events reported. In addition, stabilization of renal function and recovery trends in estimated glomerular filtration rate (eGFR) were observed in a subset of treated patients<sup>[13-15]</sup>, supporting continued clinical evaluation and advancement toward Phase III development<sup>[15]</sup>. Notably, these findings suggest a potential ability of ELIXCYTE® to attenuate the progressive decline characteristic of CKD, an organ-failure paradigm historically regarded as irreversible. In contrast to the expected trajectory under conventional standard-of-care management where patients typically experience gradual deterioration of renal function over time as fibrosis progresses, ELIXCYTE® treatment was associated with stabilization of renal parameters and prevention of further functional decline following a single administration.

Collectively, these clinical observations are consistent with the immunomodulatory, cartilage-protective, and renal-protective activities identified across the ELIXCYTE® development program and provide important translational support for its ongoing clinical advancement.

#### Conclusion

The development of ELIXCYTE® illustrates how a scientifically driven cell therapy program can integrate clinical development, mechanistic understanding, and potency assessment into a unified regenerative medicine strategy.

Supported by a robust manufacturing infrastructure, a USFDA MF, and a PIC/S GMP-compliant production process, ELIXCYTE® has established a strong foundation for scalable and standardized, off-the-shelf allogeneic cell therapy development.

The collective evidence presented in this article highlights the potential of ELIXCYTE® as a standardized allogeneic cell therapy product capable of addressing multiple chronic degenerative diseases through shared biological mechanisms, including anti-inflammation, immunomodulation, cartilage protection, and renal protection. Clinical studies in osteoarthritis and chronic kidney disease have demonstrated favorable safety profiles together with encouraging therapeutic outcomes, while ongoing mechanistic and potency studies continue to strengthen the scientific foundation underlying its development.

Taken together, the findings presented in this article demonstrate how ELIXCYTE® integrates immunomodulatory, tissue-protective, and regenerative activities to address key pathological mechanisms shared across chronic degenerative diseases. By integrating translational science, regulatory-oriented potency strategies, and clinical development, ELIXCYTE® provides a promising framework for the future advancement of regenerative medicine and cell-based therapeutics.

#### Acknowledgment

We gratefully acknowledge the principal investigators with whom we collaborated on the clinical development of ELIXCYTE® for OA and CKD.

#### Conflict of interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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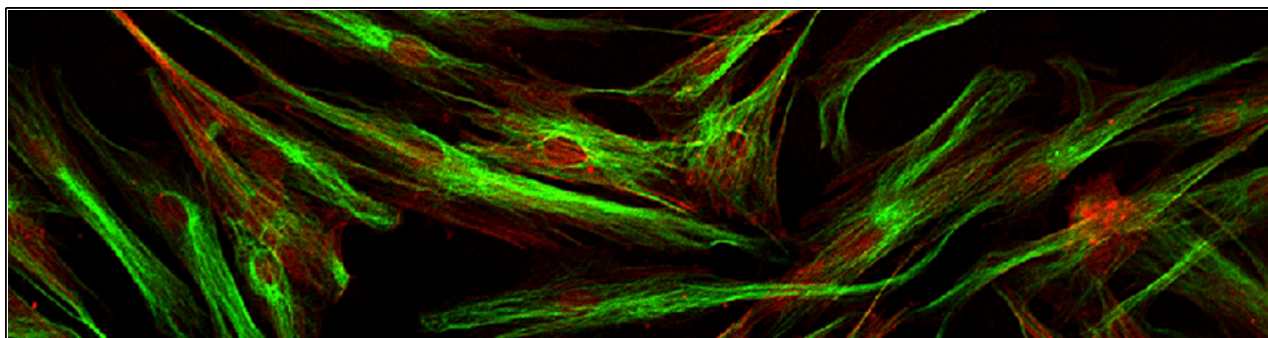


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## Beginning with the End in Mind, the Journey of Mesenchymal Stem/stromal Cell Therapy Product Development

### Abstract

**Background:** Cell therapy products are living drugs that serve as alternative therapeutic strategies for various unmet medical needs, including cancers, tissue degeneration, and immune dysregulations. To achieve global success, developers must navigate the evolving complexities of advanced therapy medicinal product (ATMP) development.

**Findings:** This review focuses on the lifecycle of cell product development. Key translational phases are discussed, including navigating regulatory pathways in major global markets, embedding Quality by Design (QbD) principles to establish the Quality Target Product Profile (QTPP), defining Critical Quality Attributes (CQAs), and scaling up manufacturing while maintaining strict Good Manufacturing Practice (GMP) compliance.

**Conclusion:** This brief review provides actionable insights into the cell therapy ecosystem, effectively bridging the gaps between early stage research and development, regional clinical development, complex regulatory strategies, and the scalability offered by specialized Contract Development and Manufacturing Organization (CDMO) partnerships.

**Keywords:** mesenchymal stem/stromal cell, quality by design, regulatory pathways

### Introduction

Cell therapies represent "living drugs" characterized by unique mechanisms of action, biological activities, and regulatory challenges that distinguish them from traditional small molecules and biologics.

### Corresponding author:

**Dr. Ling-Mei Wang** is the Chairperson and Chief Strategy Officer of **Steminent Biotherapeutics Inc.**, a pioneer in the development of mesenchymal stem cell therapies. Dr. Wang has been a driving force in advancing translational medicine and commercializing breakthrough cellular therapies for rare and incurable diseases.



Their inherent manufacturing complexity, batch-to-batch heterogeneity, and short shelf life necessitate integrated development strategies that tightly couple manufacturing, clinical development, and regulatory planning from the earliest stages.

Mesenchymal stem/stromal cells (MSCs) are abundant adult stem cells that can be isolated and culture-expanded from bone marrow, adipose tissue, and neonatal tissues. These cells exert potent immunomodulatory effects and secrete trophic factors, which have led to their approval for treating various diseases, such as acute graft-versus-host disease (e.g., TEMCELL in Japan and Ryoncil in US), osteoarthritis (e.g., CARTISTEM in Korea), and critical limb ischemia (e.g., Stempeucel in India).

There are at least three critical factors for successful MSC product development: indication selection, route of administration, and manufacturing consistency. Indication selection is intrinsically linked to clinical trial design and regional regulatory requirements, which govern parameters such as donor eligibility criteria and preclinical safety profiles.



Furthermore, donor variation and labor-intensive, large-scale production present significant hurdles for commercialization. To mitigate these risks, developers should embed QbD principles during early product development, ensuring product quality throughout the entire lifecycle. Last but not least, for biotech companies, early engagement with global professional CDMOs can effectively de-risk manufacturing challenges and product logistics. More importantly, this allows companies to remain focused on pipeline expansion and indication development, rather than allocating excessive resources to maintaining a GMP-compliant facility. In conclusion, this article introduces the concept of the cell therapy ecosystem, advocating for a transition from isolated operations to strategic collaboration to achieve global success.

### Findings

Mesenchymal stem/stromal cells (MSCs) represent a novel drug modality exhibiting multifaceted biological activities, which have been widely leveraged in clinical studies to treat a broad spectrum of conditions, including inflammatory, skeletal, neurological, cardiocerebral vascular, and respiratory diseases (1). To date, more than 1,700 clinical trials have been registered on ClinicalTrials.gov, spanning both high-prevalence conditions and rare or severe diseases. However, despite this robust pipeline, only a limited of products have successfully secured final regulatory approval and been launched into the market. To bridge this critical gap between clinical research and commercial approval, the following key considerations are essential to address.

#### 1.Strategic Product Development and Goal Definition.

Developers must first establish robust core technology platforms and comprehensively characterize the therapeutic product tailored to target indications. This involves thoroughly assessing existing unmet medical needs and defining a distinct therapeutic differentiation profile for the investigational product relative to current standard-of-care therapies. Furthermore, it is highly recommended to proactively evaluate regional healthcare infrastructures and patient access capabilities, alongside country-specific reimbursement frameworks and health economic considerations, to pre-emptively mitigate market entry barriers.

#### 2.Regional Expedited Development Programs and Clinical Trial Frameworks.

To accelerate patient access, various jurisdictions have established distinct regulatory pathways tailored to expedite the translation of cell and gene therapy (CGT) products. These frameworks offer strategic mechanisms—such as expedited reviews, rolling submissions, and priority designations—designed to compress clinical development timelines and fast-track market entry. The prominent global frameworks include:

- United States (FDA): Utilizes specialized pathways including Regenerative Medicine Advanced Therapy (RMAT) and Breakthrough Therapy designations, alongside Fast Track, Accelerated Approval, and Priority Review mechanisms to expedite unmet clinical needs. A prominent case is Ryoncil, which strategically leveraged the RMAT designation to accelerate its clinical development and Biologics License Application (BLA) regulatory review for pediatric steroid-refractory acute graft-versus-host disease.
- Europe (EMA): Leverages the PRiority MEDicines (PRIME) scheme and accelerated assessment procedures to optimize development timelines for innovative therapeutics. A pioneering example is Alofisel, which became the first allogeneic MSC product to receive marketing authorization through the EMA's advanced therapy frameworks; however, due to post-marketing strategic re-evaluations, this product's authorization has recently been withdrawn.
- Japan (PMDA): Employs the Sakigake designation system to accelerate the development and approval of regenerative therapies addressing severe and unmet medical needs. Furthermore, under Japan's PMD Act, a dedicated conditional and time-limited approval scheme is established for regenerative medicine.
- Taiwan (TFDA): Official implementation of Regenerative Medicine Dual Acts 2026, allows conditional approval for products designed for the treatment of life-threatening or severely disabling diseases, confirmed safety and preliminary efficacy in phase II clinical trials. In addition, the Ministry of Health and Welfare has initiated a pilot program, the Taiwan Regenerative Medicine Advanced Therapy (T-RMAT) framework, which is designed to facilitate early regulatory alignment, rolling reviews and guidance, with the aim of identifying and addressing potential development risks at an early stage.

#### 3.Establishing the Quality Target Product Profile and Continuous Monitoring.

Cell products are highly sensitive to environmental and processing factors that can dramatically impact their biological characteristics. Every stage of the cellular manufacturing process—including cell isolation, culture media supplementation, expansion strategies, and release criteria—is critical to successful product development. Consequently, it is highly recommended to establish a QTPP as soon as the initial Target Product Profile (TPP) is drafted (2-4). Table 1 illustrates the QbD relationship matrix that links these critical parameters. As culture media evolve (from animal-derived components to chemically defined formulations) and manufacturing technologies advance (such as 3D scaffold-based cultures and automated closed systems), developers can adopt more efficient and cost-effective strategies to refine production.

This QbD matrix serves as an essential framework to dissect key production variables, particularly when implementing manufacturing changes or executing technology transfers to CDMOs for commercial scale-up (5). Throughout this iterative process, it is vital to continuously re-examine the QbD matrix by addressing the following pivotal questions:

- Which product attributes directly impact efficacy and safety?
- Which raw materials and excipients critically affect product quality?
- Within which operational ranges is product quality consistently assured?
- Is the current manufacturing process robust enough to support commercial scalability?

In the cell therapy field, where "the process is the product," a well-designed, strictly controlled manufacturing workflow is often the ultimate key to commercial and clinical success.

**Table 1.** Integrated QbD Matrix for Cell Therapy Development and Manufacturing

| QTPP items     | Critical quality attribute         | Critical process parameter                        | Control Strategy                    |
|----------------|------------------------------------|---------------------------------------------------|-------------------------------------|
| Identity       | Morphology/ Surface markers        | Population doubling level                         | Flow cytometry                      |
| Cell expansion | Viable cells meet commercial scale | Culture conditions, pH, pO <sub>2</sub> , glucose | Design of space, material attribute |
| Purity         | Residual raw materials             | Washing cycles                                    | Release testing                     |
| Safety         | Sterility                          | Closed processing                                 | Sterility testing                   |
| Stability      | Product shelf life                 | Storage temperature                               | Stability program                   |
| Potency        | Functional assay                   | Media composition                                 | Potency assay                       |

**4. Translating Strategy into Practice: Steminent** Biotherapeutics's Global Execution. Translating these complex regulatory, clinical, and manufacturing frameworks into practical execution requires seasoned expertise. With over a decade of experience in product manufacturing and clinical development, Steminent continuously upgrades its manufacturing technologies and synchronizes with evolving regulatory standards to accelerate product advancement. By engaging clinical key opinion leaders (KOLs) early on in both Taiwan and the United States, the company has successfully completed a Phase II, double-blind, placebo-controlled trial in Taiwan and is currently preparing for a Phase II trial in the US.

Furthermore, through a strategic partnership with REPROCELL in Japan, Steminent is leveraging global resources—including advanced cell culture raw materials and smart CDMO capabilities for commercial production—to pave the way for BLA approvals. This integrated global strategy serves as a successful blueprint for the translational research of MSC products, aligning with the company's core vision: *"Better ways to treat diseases, bringing innovation to promote a better life."*

## Conclusion

MSC possess multifaceted biological functions that enable their allogeneic use in treating a diverse spectrum of complex medical conditions. While numerous clinical studies have consistently demonstrated their safety and therapeutic efficacy, translating this clinical promise into a viable commercial product remains exceptionally challenging. To enhance the probability of translational success, developers are required to engage clinical KOLs early to address true unmet medical needs and continuously align with regulatory agencies to leverage global expedited programs. Ultimately, integrating the QbD framework into cell therapy product development provides a robust lifecycle management strategy, ensuring strict batch-to-batch consistency in commercial manufacturing and paving the way toward global market success.

## Acknowledgment

The authors would like to thank the Steminent team for their efforts in collecting and summarizing the information.

## Conflict of interest

The authors declare no conflict of interest.

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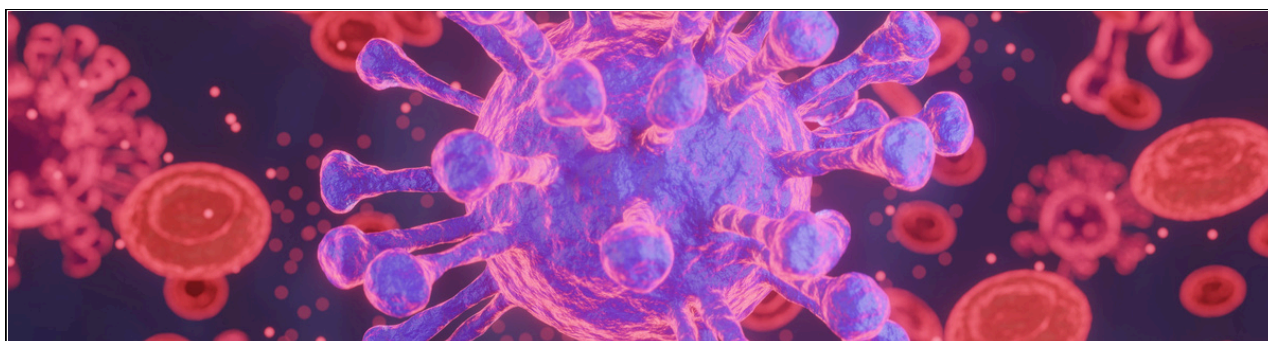


IMAGE FROM CANVA.COM

## China's CAR-T and Immune Cell Therapy CDMO Landscape: Process Development, GMP Manufacturing, and Platform-Based Global Expansion

### CDMO Process Development for CAR-T and Other Immune Cell Therapy Products

As chimeric antigen receptor T cell (CAR-T), universal CAR-T (UCAR-T), CAR-natural killer (CAR-NK), T cell receptor-engineered T cell (TCR-T), tumor-infiltrating lymphocyte (TIL), and other immune cell therapy products progressively advance from bench research toward clinical trials and commercial manufacturing, the cell and gene therapy (CGT) contract development and manufacturing organization (CDMO) industry in China is no longer limited to a conventional contract-manufacturing model. Instead, it is gradually evolving into an integrated service model covering technology transfer, process development, analytical method development, Good Manufacturing Practice (GMP) manufacturing, quality testing, Investigational New Drug (IND) application support, and commercial scale-up.

Taking Porton Advanced as an example, according to its official materials, Porton Advanced is positioned as an end-to-end clinical research organization (CRO) and CDMO platform for gene and cell therapy, with services covering technology transfer, non-registrational clinical sample manufacturing, process development, analytical method development, cGMP manufacturing, testing services, IND application support, and New Drug Application (NDA) support. Its stated service scope also explicitly covers a diverse range of cell and gene therapy products.

Regarding CDMO process development experience for CAR-T and other immune cell therapy products, Porton Advanced and OBiO both demonstrate relatively broad product coverage and clinical translation experience.

Since establishing its first cell therapy cGMP production line, Porton Advanced has secured 26 global IND approvals from the NMPA, FDA, and Medsafe, with 12 ongoing Phase I/II advanced therapy medicinal product (ATMP) projects. Its official CDMO case portfolio also includes EpCAM CAR-T, B7-H3 CAR-T for glioma, NKG2DL CAR-T for solid tumors, TCR-T, and other projects. OBiO states that its CGT CDMO services can support technical research, process development, and GMP manufacturing for CAR-T, UCAR-T, NK, CAR-NK,  $\gamma\delta$  T cell, TIL, regulatory T cell (Treg), and dendritic cell (DC) therapy products. These examples suggest that OBiO's platform positioning is not restricted to a single CAR-T product but extends to multiple categories of immune cell therapies.

### Viral Vector and Plasmid DNA Supply as a Critical Bottleneck

The availability of viral vectors, including lentiviral vectors, as well as plasmid DNA, remains a critical bottleneck for the stable progression of CAR-T and other genetically modified cell therapy products into clinical trials. According to OBiO's official materials, its gene therapy CDMO services cover adeno-associated virus (AAV), lentiviral, and adenoviral vectors and can also support major gene therapy products, such as plasmids, oncolytic viruses, and CAR-T products. Its viral vector process development integrates high-throughput process development, Design of Experiments (DoE), and Quality by Design (QbD) concepts, and the company has accumulated hundreds of process development reports including plasmids, lentiviral vectors, AAV, multiple oncolytic viruses, and CAR-T cell therapy products.

ProBio, the CDMO arm of GenScript, positions itself as an end-to-end CDMO service provider from drug discovery to commercialization, covering biologics, cell and gene therapy, plasmids, viral vectors, and mRNA vaccines. The company reports that, since 2017, it has supported more than 150 IND approvals across the United States, Europe, and the Asia-Pacific region. In addition, ProBio signed a memorandum of understanding (MOU) with the Korean CAR-T company Curocell for viral vector manufacturing, including the development, production, and clinical trial support of viral vectors required for next-generation CAR-T therapies. ProBio's announcement also directly notes that shortages in GMP viral vector facilities may delay the development of CAR-T and other gene therapies.

#### **GMP Manufacturing Challenges for Autologous and Allogeneic Immune Cell Therapy Products**

The GMP manufacturing challenges for immune cell therapy products primarily lie in focusing in batch-to-batch variability, closed-system operations, cleanroom configuration, cross-contamination control, and flexible production capacity. According to Porton Advanced's official materials, the company operates multiple closed-system cGMP production lines. These lines are designed to support autologous cell products, allogeneic cell products, and various cell therapy products that require extensive closed-system operations. Its autologous cell production lines are equipped with automated separation, culture, and concentration systems, and each production line is configured with Grade B and Grade A cleanrooms for modularized cGMP production. Hillgene also emphasizes that its HiCellx® platform is a fully closed and automated cell process development platform, enabling flexible adaptation to the production and testing requirements of different cell products. These examples suggest that CDMO providers in China are responding to the manufacturing challenges of autologous and universal cell therapy products through closed-system and modularized manufacturing strategies.

In the context of digitalized manufacturing, automation, closed-system platforms, and single-use processing technologies have become clear trends in the industry. OBiO states that it has developed a fully closed and automated purification process using single-use production equipment for end-to-end closed pipeline operations. This approach is intended to improve purification efficiency and aseptic manufacturing capability while achieving high throughput, high yield, and high-quality assurance. Hillgene highlights its HiCellx® fully closed cell platform, HiLenti® suspension serum-free lentiviral platform, and HiPlas™ nucleic acid platform, and further states that its closed cell platform is applicable to the manufacturing of both autologous and universal cell products. Therefore, based on public official information, the current focus of CDMO industry for immune cell therapy in China is not merely the expansion of production capacity. Rather, the industry is building comprehensive infrastructure that supports CAR-T and next-generation immune cell therapies from early -

development to commercial manufacturing through the integration of closed systems, automation, single-use technologies, DoE, QbD, CMC (Chemistry, Manufacturing, and Controls) strategies, and international regulatory submission experience.

#### **Industry Development Trends**

The development trajectory of CGT CDMO industry in China is shifting from single-point service provision toward multifaceted, cross-platform, cross-regional, and internationalized one-stop solutions. In its 2026 official announcement, Porton Advanced stated that it had established a strategic collaboration with T&L Biotechnology to provide global CGT clients with an integrated and seamless solution spanning core raw materials, process development, and scale-up manufacturing. The same announcement also stated that Porton Advanced had established CRO/CDMO platforms for plasmids, viral vectors, cell therapy, gene therapy, and nucleic acid therapeutics. The company had also built 10 viral vector production lines and 12 GMP cell therapy production lines, and had also helped clients obtain clinical trial approvals in China, the United States, New Zealand, and other countries. Hillgene also states that its platforms have supported multiple CAR-T, TCR-T, CAR-NK, and hematopoietic stem cell (HSC) products and have obtained more than 24 clinical trial approvals from different regulatory agencies, including the NMPA, EMA, and FDA. These developments indicate that Chinese CDMO companies have begun to position global supply capabilities and multiregional regulatory submission experience as core competitive advantages.

#### **Conclusion**

In summary, China's CAR-T and immune cell therapy CDMO industry is at a critical transition point, moving from rapid expansion toward higher quality standards and international competitiveness. In the future, as process standardization, quality systems, and cross-regional regulatory experience continue to mature, Chinese CGT CDMO providers with integrated platform capabilities and global service networks will be better positioned to play important roles in the global cell and gene therapy value chain. These capabilities may further accelerate the clinical translation and commercialization of next-generation immune cell therapies.

#### **Disclaimer**

This article was compiled and written based on publicly available information from the official websites and related official materials of the companies mentioned above. The summarized public information is intended solely for academic discussion and reference. Although the authors have made every effort to verify the content, all data and descriptions should ultimately be interpreted according to the most recent updates issued by the original publishing organizations.





IMAGE FROM CANVA.COM

# From AI Agents to Automated Cell Factories: How Artificial Intelligence Is Reshaping Drug Development, Digital Biology, and Cell Therapy

## Introduction

Over the past several years, generative artificial intelligence has primarily been used to produce text, images, and computer code in response to user instructions. As large language models gain stronger reasoning and tool-use capabilities, AI is evolving from a passive chatbot into an AI agent capable of receiving a goal, breaking it into smaller tasks, retrieving information, operating external software, evaluating results, and adjusting its strategy based on feedback. An AI agent is therefore more than an advanced language model. A complete agentic system also requires memory, workflow orchestration, external tools, and a secure execution environment. [1].

## From Digital Assistants to Scientific Partners

AI agents are beginning to move beyond literature summarization and administrative support. A representative example is Robin, a multi-agent scientific discovery system reported in Nature. Robin integrates literature retrieval, hypothesis generation, experimental planning, and data analysis into an iterative research cycle. Human researchers conduct the physical experiments and return the results to the system, which interprets the data and proposes updated hypotheses [2].

Nevertheless, current AI scientists should not be viewed as autonomous replacements for human researchers. Biological research involves tacit knowledge, undocumented experimental failures, biological variability, and practical limitations that may not be represented in training data.

AI may also generate incorrect references, overlook data bias, or propose experiments that are theoretically plausible but difficult to execute. A more realistic role for AI is therefore that of a co-scientist: AI can continuously search, calculate, simulate, and generate candidate solutions, while human researchers determine their biological significance and decide which experiments should be performed.

## Nemotron and BioNeMo: Reasoning With Biological Tools

Within NVIDIA's architecture, Nemotron provides the reasoning foundation that enables an agent to understand objectives, plan tasks, and select appropriate tools. Nemotron is not a complete agent by itself; it operates with orchestration frameworks and secure execution environments that manage memory, tool access, permissions, and workflow control [3].

General-purpose language models can understand biomedical literature but do not necessarily know how to correctly perform protein-structure prediction, molecular docking, genomic analysis, or therapeutic design. The BioNeMo Agent Toolkit addresses this limitation by packaging biological and chemical models, libraries, and computational workflows into tools that AI agents can call [4]. In this framework, the reasoning model determines what should be done, while BioNeMo provides the domain-specific tools needed to perform the scientific computation. These tools include protein-structure prediction, molecular docking, generative chemistry, genomic analysis, protein design, biomarker discovery, and virtual screening.

The main advance is not simply faster computation. BioNeMo can connect tools that researchers previously operated separately across different software packages and data formats. An agent may gather evidence, prepare model inputs, run computational experiments, compare outputs, and recommend the next analytical step within a repeatable workflow. However, these outputs remain computational hypotheses and must still be confirmed through biochemical assays, cell experiments, animal studies, and clinical validation.

## Digital Biology and Drug Development

Digital biology converts DNA, RNA, proteins, cellular images, single-cell omics, spatial data, and clinical phenotypes into computational representations that AI models can learn from and simulate. Earlier biological models were usually designed for individual tasks, such as predicting protein structures or classifying cell types. New biological foundation models attempt to learn broader biological patterns and predict gene perturbations, drug responses, and changes in cellular states. This development has contributed to the concept of the AI virtual cell [5,6].

Virtual-cell models may help researchers simulate how cells respond to genetic modification, environmental changes, or drug exposure. However, they remain incomplete representations of real cells. Cellular behavior is influenced by culture medium, extracellular matrices, cell density, mechanical signals, oxygen levels, cell-cell interactions, and time—factors that are often missing or incompletely recorded in existing datasets. Virtual cells should therefore be regarded as tools for generating hypotheses and narrowing the experimental search space rather than as substitutes for biological experiments. AI agents could simulate gene knockouts or drug treatments, identify the most informative conditions, and recommend validation using CRISPR assays, organoids, or cell cultures. Experimental results could then be returned to the model, forming a closed design-build-test-learn cycle [7].

In early drug discovery, agents could integrate biomedical literature, disease databases, genomic evidence, protein-interaction networks, and single-cell data to identify potential therapeutic targets and biomarkers. Candidate targets could then be passed to structural-analysis and virtual-screening agents. During compound design, agents could combine protein-structure prediction, molecular generation, docking, molecular dynamics, and ADMET models. Rather than relying on one model to generate a “perfect drug,” multiple specialized tools could iteratively optimize potency, selectivity, solubility, toxicity, and synthetic feasibility.

In preclinical and clinical development, agents may also assist with toxicology review, dose-response analysis, biomarker identification, patient stratification, clinical-trial matching, and statistical programming. When AI-generated evidence is used to support

decisions regarding the safety, effectiveness, or quality of a drug or biological product, however, its context of use must be clearly defined. The Good AI Practice principles jointly developed by the U.S. Food and Drug Administration and the European Medicines Agency emphasize human-centered design, risk-based assessment, data governance, performance evaluation, documentation, and life-cycle management for AI used in drug development [8].

## The Special Value of AI Agents in Cell Therapy

Unlike small-molecule drugs with relatively stable chemical structures, cell-therapy products are living populations that change over time and in response to their environment. Donor or patient variability, starting-cell characteristics, culture conditions, cell density, genetic modification, metabolic state, and harvest timing can all influence the final product. Cell therapy is therefore particularly suitable for multimodal AI systems capable of integrating cellular images, environmental parameters, metabolite concentrations, flow-cytometry results, gene-expression profiles, and potency assays.

The first potential application is cell and product design. AI can integrate single-cell transcriptomics, protein expression, and functional assays to identify cellular states associated with therapeutic activity, persistence, differentiation capacity, immunomodulation, or exhaustion. In CAR-T development, AI-guided design has already been experimentally explored to improve CAR durability, reduce antigen escape, and optimize antitumor function [9].

The second application is process development and parameter optimization. An agent could analyze relationships between critical process parameters and critical quality attributes throughout cell culture. Researchers have used live-cell bright-field imaging and machine learning to recognize cellular states during pluripotent stem-cell differentiation, predict outcomes, and adjust culture conditions to reduce variability between cell lines and production batches [10].

The third application is non-destructive, real-time quality monitoring. Conventional cell-product testing often requires sampling, staining, or destruction of cells, while functional potency assays may take several days. Image-based AI can instead examine the morphology, arrangement, movement, and heterogeneity of living cells [11].

In the future, an AI agent could continuously monitor an entire culture process rather than analyze one image at a time. When abnormal morphology, confluence, or growth kinetics are detected, the agent could integrate manufacturing records, environmental parameters, metabolic measurements, and imaging data before recommending additional sampling or deviation investigation.

In a GMP environment, the data used by the agent, model version, recommendations, and subsequent actions would need to remain traceable. Process changes and final batch-release decisions should remain under the responsibility of qualified personnel.

## From N1X to Physical AI and Automated Cell Factories

Before its formal launch, NVIDIA's Arm-based AI PC platform was widely discussed in technology media under the name N1X. NVIDIA officially introduced the platform as the RTX Spark Superchip, which combines an Arm-based CPU, a Blackwell GPU, and unified memory to support local AI agents and large models [12].

For biomedical research, local agent computing could potentially allow sensitive experimental or patient data to be analyzed near laboratory instruments rather than being transferred entirely to the cloud. Large-scale model training and molecular screening would still require data-center infrastructure, but selected image-analysis, monitoring, and agent workflows could run locally. While N1X or RTX Spark brings agents closer to researchers and instruments, Cosmos 3 extends AI into the physical environment. Cosmos 3 combines visual reasoning, world generation, and action prediction, allowing it to function as a vision-language model, world model, or foundation for robotic control [13].

Its role is not to analyze DNA or proteins directly. Instead, it can help robots understand physical environments, predict the consequences of actions, and practice tasks in simulation before transferring those skills to real equipment. In an automated cell-therapy facility, Physical AI could support the transport of culture vessels, tubing connections, sampling, centrifugation, medium exchange, microscopy, and cold-chain logistics. Because trial-and-error learning in sterile or GMP environments is costly and risky, developers can first create a laboratory digital twin in which equipment, robotic arms, consumables, and workflow layouts are simulated.

Multiply Labs has used NVIDIA Omniverse to construct digital twins of cell-therapy manufacturing environments and Isaac Sim to test robotic laboratory operations through thousands of virtual iterations before real-world deployment.

## Developments in Taiwan

Publicly documented NVIDIA collaborations in Taiwan currently focus more on clinical agents, smart hospitals, and medical robotics than on the direct adoption of BioNeMo for drug discovery. Foxconn has integrated NVIDIA technologies including Nemotron, NemoClaw, Omniverse, and Isaac into its healthcare platforms.

Its CoDoctor and CoDoClaw systems coordinate specialized clinical agents for applications such as breast imaging, electrocardiography, retinal imaging, and coronary-artery analysis [14]. Foxconn's Nurabot nursing collaborative robot has also completed field validation and is being introduced into hospitals and long-term care settings.

Nurabot supports repetitive clinical tasks such as medication and specimen transport, demonstrating how Physical AI can be integrated into real healthcare workflows [15]. Compal Electronics is developing the POLYMEDX smart-hospital platform with NVIDIA technologies. POLYMEDX integrates AI orchestration, digital twins, edge AI, Omniverse, Isaac ROS, and robotic systems to simulate, validate, and deploy hospital workflows [16].

These projects are not yet equivalent to BioNeMo-based drug discovery or automated cell-therapy manufacturing. Nevertheless, they demonstrate Taiwan's growing ability to integrate AI agents, simulation, robotics, and healthcare operations. The same infrastructure could eventually be extended to laboratory automation and advanced biomanufacturing.

## Conclusion

The greatest impact of AI agents on drug development and cell therapy may not come from accelerating one isolated analysis. Their broader value lies in connecting literature review, computational modeling, experimental design, cell culture, quality monitoring, and robotic operations into a continuously learning workflow. A future research environment may involve human scientists defining research questions and acceptable risk boundaries, AI agents organizing information and planning workflows, and Physical AI systems performing selected laboratory operations. In medicine and cell therapy, the most valuable AI agent will not be an uncontrolled autonomous scientist, but a traceable and reliable digital research partner whose evidence, actions, and limitations can be reviewed by human experts.

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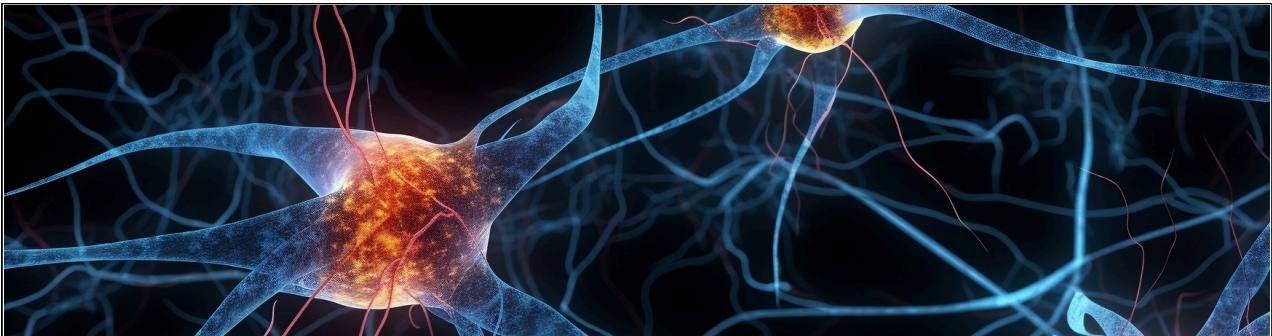


IMAGE FROM CANVA.COM

# AMCHEPRY®: The First iPSC-Derived Cell Therapy Marks a New Era of Regenerative Medicine for Parkinson's Disease

## Introduction

Since the development of induced pluripotent stem cell (iPSC) technology by Yamanaka and colleagues in 2006, regenerative medicine has undergone a remarkable transformation. Unlike embryonic stem cells, iPSCs are generated by reprogramming adult somatic cells into pluripotent cells, thereby avoiding ethical concerns associated with embryo use while retaining the capacity to differentiate into multiple cell types [1]. Consequently, iPSCs have become one of the most promising platforms for regenerative medicine and cell-based therapies. During the past two decades, considerable efforts have focused on translating iPSC technology into clinical applications for neurodegenerative disorders, retinal diseases, cardiovascular diseases, and diabetes. However, challenges including manufacturing consistency, tumorigenicity, immune rejection, and regulatory approval have limited the number of clinically approved iPSC-derived products [2].

Japan has played a leading role in the clinical translation of iPSC technology through continuous governmental support, the establishment of HLA-matched iPSC stock programs, and the development of dedicated regulatory pathways for regenerative medicine [3]. Against this background, AMCHEPRY® (raguneprocel), developed jointly by Sumitomo Pharma and the Center for iPS Cell Research and Application (CiRA), became the first approved iPSC-derived dopaminergic progenitor cell therapy for Parkinson's disease in Japan in 2026[3]. Its approval represents not only a milestone in regenerative medicine but also a paradigm shift from symptomatic treatment toward cell replacement therapy.

Unlike conventional pharmacological therapies that temporarily restore dopamine levels, AMCHEPRY® delivers iPSC-derived dopaminergic progenitor cells directly into the striatum, aiming to replace degenerated neurons, reconstruct neural circuits, and achieve sustained functional recovery [4]. Therefore, the significance of AMCHEPRY® extends beyond the approval of a novel therapeutic product and highlights the clinical feasibility of iPSC-based regenerative medicine.

## Parkinson's Disease (PD)

Parkinson's disease is the second most common neurodegenerative disorder worldwide and one of the fastest-growing neurological diseases associated with population aging [5]. It is estimated that more than 25 million people currently live with PD globally, and the prevalence is expected to more than double by 2050 [6]. In addition to progressive motor disability, PD imposes substantial socioeconomic and healthcare burdens.

The hallmark pathology of PD is the progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta, resulting in dopamine depletion in the nigrostriatal pathway. Reduced dopamine disrupts basal ganglia circuitry, ultimately leading to the characteristic motor symptoms of bradykinesia, resting tremor, rigidity, and postural instability. Because clinical manifestations usually become apparent only after approximately half of dopaminergic neurons have already been lost, substantial neurodegeneration has typically occurred by the time of diagnosis [7].



In addition to neuronal loss, abnormal aggregation of  $\alpha$ -synuclein represents another pathological hallmark of PD. Misfolded  $\alpha$ -synuclein oligomers induce mitochondrial dysfunction, oxidative stress, impaired protein degradation, and chronic neuroinflammation, thereby accelerating neuronal degeneration. Increasing evidence also suggests that  $\alpha$ -synuclein may spread through a prion-like mechanism, contributing to disease progression throughout interconnected neural networks. Consequently, PD is now recognized as a multifactorial neurodegenerative disorder involving protein misfolding, neuroinflammation, mitochondrial dysfunction, and impaired cellular homeostasis, rather than merely a dopamine-deficiency syndrome [8,9].

Besides motor dysfunction, patients frequently experience non-motor manifestations including hyposmia, constipation, sleep disturbances, autonomic dysfunction, depression, anxiety, and cognitive impairment. Many of these symptoms precede motor manifestations by several years, highlighting the prolonged prodromal phase of PD and emphasizing the need for disease-modifying therapies capable of intervening before extensive neuronal loss occurs [8,9].

### Current Therapeutic Strategies and Their Limitations

Levodopa has remained the cornerstone of Parkinson's disease (PD) treatment since its introduction in the 1960s [10]. After crossing the blood-brain barrier, levodopa is converted into dopamine and effectively alleviates motor symptoms, particularly bradykinesia and rigidity. To improve therapeutic efficacy and reduce peripheral metabolism, levodopa is commonly administered with carbidopa or benserazide and combined with dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, or catechol-O-methyltransferase (COMT) inhibitors. Nevertheless, long-term treatment is frequently complicated by motor fluctuations, dyskinesia, and the "on-off" phenomenon, which gradually diminish clinical benefits [11].

For patients with inadequate medical control, deep brain stimulation (DBS) has become an established surgical option. Electrical stimulation of the subthalamic nucleus or globus pallidus interna can improve motor symptoms and reduce medication requirements. However, neither pharmacological therapy nor DBS prevents the progressive degeneration of dopaminergic neurons, and both have limited effects on non-motor manifestations such as cognitive decline, autonomic dysfunction, and gait impairment [12].

Recent therapeutic development has shifted toward disease-modifying approaches, including anti- $\alpha$ -synuclein immunotherapy, gene therapy, RNA-based therapeutics, and small molecules targeting protein aggregation [13]. Although promising in preclinical studies, most candidates have yet to demonstrate significant clinical benefits in large-scale trials. Consequently, current therapies remain primarily symptomatic rather than restorative.

These limitations have renewed interest in cell replacement therapy. Early transplantation of fetal ventral mesencephalic tissue demonstrated proof-of-concept but was hindered by ethical concerns, limited tissue availability, and inconsistent outcomes. The emergence of induced pluripotent stem cell technology has largely overcome these obstacles by providing a renewable and standardized cell source [14].

Current strategies preferentially utilize iPSC-derived dopaminergic progenitor cells rather than mature neurons, as progenitor cells exhibit superior survival, integration, and functional maturation after transplantation. This scientific foundation ultimately led to the development of AMCHEPRY®, the first clinically approved iPSC-derived dopaminergic progenitor cell therapy for Parkinson's disease. AMCHEPRY® is an allogeneic iPSC-derived dopaminergic progenitor cell therapy developed by Sumitomo Pharma for the treatment of Parkinson's disease. It is the first commercially approved iPSC-derived regenerative medicine product for PD and is administered through stereotactic bilateral transplantation into the putamen. Unlike conventional pharmacological therapies that temporarily restore dopamine levels, AMCHEPRY® aims to replace degenerated dopaminergic neurons and reconstruct the nigrostriatal pathway through cell replacement therapy [4]. The product consists of clinical-grade ventral midbrain dopaminergic progenitor cells manufactured under good manufacturing practice (GMP) conditions using HLA-matched allogeneic iPSC cell lines.

### Development and Clinical Translation of AMCHEPRY®

AMCHEPRY® is the world's first approved iPSC-derived dopaminergic progenitor cell therapy for Parkinson's disease. Its development originated from long-term research conducted at the CiRA, Kyoto University, which established robust protocols for generating clinical-grade ventral midbrain dopaminergic progenitor cells from human iPSCs. Compared with mature dopaminergic neurons, these progenitor cells exhibit greater survival, neuronal maturation, and integration capacity after transplantation, making them the preferred cell source for PD cell replacement therapy.

To facilitate clinical translation, Sumitomo Pharma collaborated with CiRA to establish a standardized GMP production platform. The manufacturing process includes iPSC bank establishment, neural differentiation, cell purification, and comprehensive quality control, including sterility testing, chromosomal stability, cell identity, viability, and residual undifferentiated cell analysis to minimize tumorigenic risk. Consistent with the concept that "the process is the product," stringent manufacturing control is considered essential for ensuring product quality and safety [4].

Unlike conventional pharmacological therapies, AMCHEPRY® is administered through stereotactic neurosurgery rather than oral or intravenous delivery. iPSC-derived dopaminergic progenitor cells are transplanted bilaterally into the putamen, where they progressively differentiate into mature dopaminergic neurons, express tyrosine hydroxylase (TH), dopamine transporter (DAT), and vesicular monoamine transporter 2 (VMAT2), and subsequently establish functional synaptic connections with host neurons. Besides dopamine replacement, transplanted cells may also secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), potentially promoting neuronal survival and neural plasticity [4].

Preclinical studies in non-human primates demonstrated long-term graft survival, neuronal maturation, functional motor improvement, and an absence of tumor formation, providing the rationale for subsequent clinical studies. Early phase I/II clinical trials evaluated the safety and preliminary efficacy of bilateral stereotactic transplantation in patients with moderate to advanced PD. Clinical outcomes were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), magnetic resonance imaging (MRI), positron emission tomography (PET), and daily motor fluctuations. Initial results demonstrated favorable safety profiles without product-related serious adverse events or tumor formation. Improvements in UPDRS motor scores, reduced daily off-time, and increased dopaminergic activity detected by PET suggest successful graft survival and functional integration. Nevertheless, because current clinical evidence is based on relatively small cohorts with limited follow-up, long-term efficacy and durability remain to be established through larger post-marketing studies [4].

As the first commercially available iPSC-derived therapy for PD, AMCHEPRY® represents a milestone in regenerative medicine by shifting treatment from symptomatic dopamine replacement toward neuronal reconstruction. Despite encouraging early results, long-term monitoring of graft survival, immune compatibility, tumorigenicity, and sustained clinical benefit remains essential to fully define its therapeutic value.

## Clinical Perspective and Future Directions

The approval of AMCHEPRY® highlights Japan's leadership in regenerative medicine. In addition to scientific advances in iPSC technology, Japan has established a dedicated regulatory framework for regenerative medical products through the Pharmaceuticals and Medical Devices Act (PMD Act) and the Act on the Safety of Regenerative Medicine. Unlike conventional pharmaceuticals, regenerative therapies may receive conditional and time-limited approval based on preliminary evidence of safety and probable clinical benefit, followed by post-marketing surveillance to confirm long-term efficacy and safety. This regulatory pathway has accelerated clinical translation while maintaining continuous safety monitoring.

As the first approved iPSC-derived therapy for Parkinson's disease, AMCHEPRY® represents an important milestone in translating stem cell research into clinical practice. Its approval demonstrates that standardized iPSC manufacturing, GMP production, and rigorous quality control can support commercialization of regenerative medicine products. More importantly, it shifts the therapeutic concept of Parkinson's disease from symptomatic dopamine replacement toward neuronal reconstruction through cell replacement therapy [4].

Nevertheless, several challenges remain. Long-term graft survival, immune compatibility, durability of clinical benefit, and potential late-onset adverse events require continued investigation through post-marketing studies [15]. In addition, Parkinson's disease involves complex pathological processes beyond dopaminergic neuron loss, including  $\alpha$ -synuclein aggregation, neuroinflammation, and mitochondrial dysfunction, suggesting that cell replacement alone may not completely halt disease progression.

Despite these limitations, AMCHEPRY® establishes a new paradigm for regenerative medicine and provides a foundation for future iPSC-derived therapies targeting neurological and other degenerative diseases. Continued advances in stem cell biology, manufacturing technologies, and clinical evaluation are expected to further expand the role of regenerative medicine in clinical practice.

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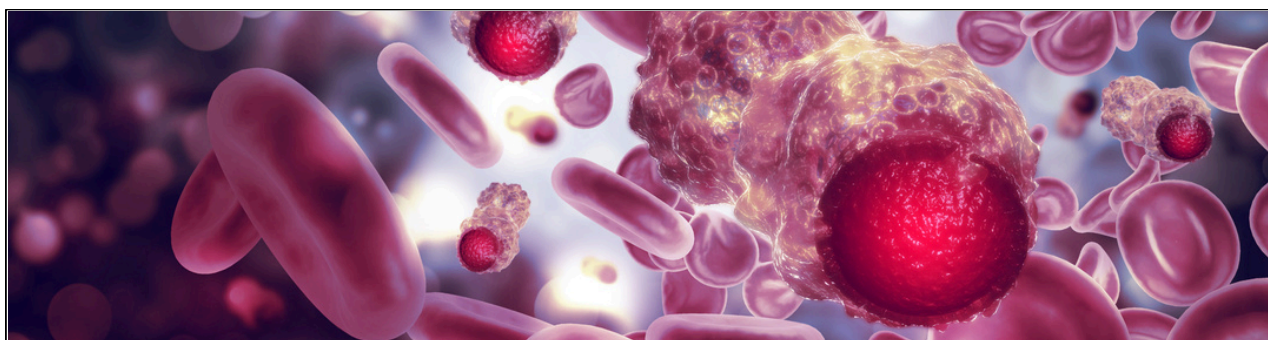


IMAGE FROM CANVA.COM

## From Pluripotency to Patients: Current Progress in iPSC-Based Clinical Trials

### Introduction

Induced pluripotent stem cells (iPSCs) were first generated from mouse cells in 2006 and human cells in 2007 by reprogramming differentiated somatic cells back to a pluripotent state [1, 2]. Because iPSCs can proliferate extensively and differentiate into many specialized cell types, they offer a potentially renewable source of cells for research and clinical manufacturing [3]. Their clinical translation now includes direct cell transplantation, standardized production of blood or immune cells, and the use of patient-derived disease models to guide drug trials [3, 4]. The central question is therefore no longer whether iPSC-derived cells can be administered to patients, but whether they can provide durable and clinically meaningful benefits with acceptable long-term risks [3, 5].

Ophthalmology was the first field to enter human studies, partly because cells can be delivered locally and monitored directly by imaging [3]. In 2014, a Japanese team transplanted an autologous iPSC-derived retinal pigment epithelium sheet into a patient with neovascular age-related macular degeneration; no serious transplant-related adverse events were observed, although vision remained stable rather than clearly improving [6]. Later studies evaluated HLA-matched allogeneic retinal pigment epithelial cells, retinal organoid sheets for retinitis pigmentosa, and corneal epithelial sheets for limbal stem-cell deficiency. These small studies generally supported short-term safety and graft survival, but their sample sizes and uncontrolled designs were insufficient to establish visual efficacy [7-9]. A US phase I/IIa study is now evaluating autologous iPSC-derived retinal pigment epithelial cells for geographic atrophy associated with age-related macular degeneration [10].

The nervous system has become another major area of development. In a Japanese phase I/II study, seven patients with Parkinson's disease received bilateral transplantation of allogeneic iPSC-derived dopaminergic progenitors and were followed for 24 months. No serious adverse events or tumorigenic overgrowth were reported, while motor examinations and brain imaging showed encouraging signals in some participants. Patient-reported and daily-function outcomes did not improve consistently, and the open-label, uncontrolled design prevents a definitive conclusion about efficacy [11].

In March 2026, Japan granted conditional and time-limited approval to AMCHPEPRY (raguneprocil), the dopaminergic progenitor product used for Parkinson's disease. It became the first iPSC-derived regenerative medicine product to receive marketing authorization, but post-marketing clinical study and surveillance remain necessary to obtain full approval [12]. Autologous iPSC-derived dopamine neurons are also being evaluated in a small US phase I study, while a separate US study is assessing the allogeneic CTI-DAP001 product [13, 14]. Japan also completed a four-patient clinical study of iPSC-derived neural stem/progenitor cells for subacute spinal cord injury. All four patients completed one year of follow-up, and no serious adverse events causally related to the therapy were reported; efficacy findings remain preliminary [15, 16]. Japan also conditionally approved RiHEART, an allogeneic iPSC-derived cardiomyocyte-sheet product for severe ischemic heart failure, in March 2026 [17].

Its supporting clinical study included eight patients without a concurrent control group, so post-marketing research must determine the durability of benefit and the contribution of surgery, immunosuppression and patient selection [18]. The simultaneous approvals of AMCHPEY and RiHEART represented a regulatory milestone, but they were granted through Japan's conditional regenerative-medicine pathway rather than conventional large confirmatory randomized trials [12, 17].

Clinical development has expanded beyond the eye, brain and heart. In 2024, investigators reported that the first participant receiving autologous chemically induced pluripotent stem-cell-derived islets for type 1 diabetes became insulin independent from day 75 and maintained near-normal glycemic control at one year. This was an important demonstration of biological function, but it remained a single-patient report, and the participant was already receiving immunosuppression following a previous liver transplant [19]. In the iPLAT study, autologous iPSC-derived platelets were administered to one patient with platelet-transfusion refractoriness; the primary safety objective was met, but no clear post-transfusion platelet-count increase was demonstrated [20].

iPSCs are also being developed as renewable manufacturing platforms. CYP-001, an allogeneic iPSC-derived mesenchymal stromal-cell product, initially showed manageable safety and an encouraging response rate in a 15-patient phase I study of steroid-resistant acute graft-versus-host disease [21, 22]. However, a subsequent randomized, placebo-controlled phase II study involving 65 patients did not meet its primary efficacy endpoint in 2026 [23]. This result illustrates why encouraging signals from small uncontrolled studies must be confirmed in comparative trials [5, 23].

FT516, an off-the-shelf engineered iPSC-derived natural killer-cell product, was evaluated with an anti-CD20 antibody and interleukin-2 in 55 patients with relapsed or refractory B-cell lymphoma. No dose-limiting toxicity was reported and the objective response rate was 58%, although the uncontrolled combination-therapy design did not isolate the contribution of FT516 [24]. FT819, an off-the-shelf iPSC-derived CD19 CAR-T-cell product, is currently being evaluated in systemic lupus erythematosus and other B-cell-mediated autoimmune diseases [25]. These programs demonstrate the potential use of iPSCs as standardized manufacturing platforms for immune-cell medicines [24, 25].

iPSCs can also influence clinical trials without being transplanted. Patient-derived iPSC motor neurons were used to identify ropinirole as a candidate treatment for amyotrophic lateral sclerosis. In a subsequent 20-participant phase I/IIa trial, adverse events were similar between ropinirole and placebo, but decline in the principal functional scale was not significantly different during the double-blind period [4].

**Table 1.** Current Clinical Progress of iPSC-Based Therapies

| Therapeutic area                 | iPSC-derived product or approach       | Representative human evidence                                                                                              | Status                                                                         | Reference  |
|----------------------------------|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------|
| Age-related macular degeneration | Autologous or HLA-matched RPE cells    | One autologous and five HLA-matched recipients; generally tolerated, with variable visual outcomes                         | Early clinical studies completed; a US geographic-atrophy study remains active | [6, 7, 10] |
| Retinitis pigmentosa             | Retinal organoid sheets                | Two recipients followed for two years, with stable graft survival                                                          | Early clinical evaluation                                                      | [8]        |
| Limbal stem-cell deficiency      | Allogeneic corneal epithelial sheets   | Four recipients; no serious treatment-related adverse events, with variable clinical improvement                           | Early clinical evaluation                                                      | [9]        |
| Parkinson's disease              | Allogeneic dopaminergic progenitors    | Seven recipients; no serious graft-related events or tumor growth, with improvement in some patients                       | AMCHPEY conditionally approved in Japan                                        | [11, 12]   |
| Parkinson's disease              | Autologous neurons or CT1-DAP001       | Small phase I or I/II safety studies                                                                                       | US trials ongoing                                                              | [13, 14]   |
| Spinal cord injury               | Neural stem/progenitor cells           | Four recipients completed transplantation and one-year follow-up; no causally related serious adverse events were reported | Early clinical study completed; efficacy remains preliminary                   | [15, 16]   |
| Ischemic heart failure           | Cardiomyocyte sheets                   | Small uncontrolled clinical study                                                                                          | RiHEART conditionally approved in Japan                                        | [17, 18]   |
| Type 1 diabetes                  | Autologous CIPSC-derived islets        | One patient became insulin-independent, while receiving pre-existing immunosuppression                                     | Single-patient evidence                                                        | [19]       |
| Thrombocytopenia                 | iPSC-derived platelets                 | One patient treated safely, without a clear platelet-count increase                                                        | Proof-of-concept                                                               | [20]       |
| Acute GvHD                       | iPSC-derived mesenchymal stromal cells | Phase I safety was encouraging, but phase II did not meet its primary efficacy endpoint                                    | Efficacy remains unconfirmed                                                   | [21-23]    |
| B-cell lymphoma                  | FT516 iPSC-derived NK cells            | Phase I combination study reported a 58% overall response rate among 55 treated patients                                   | Early-phase clinical development                                               | [24]       |
| Autoimmune disease               | FT819 iPSC-derived CD19 CAR-T cells    | Phase I study in lupus and other B-cell-mediated diseases                                                                  | Recruiting/ongoing                                                             | [25]       |
| Amyotrophic lateral sclerosis    | iPSC-guided ropinirole development     | Twenty-patient trial did not show a significant primary clinical benefit                                                   | Drug-development application, not cell transplantation                         | [4]        |



The study showed that iPSC models can generate therapeutic hypotheses and potential biomarkers but cannot replace adequately powered clinical endpoints [4, 5]. Current evidence shows that diverse iPSC-derived products can be manufactured and administered through multiple routes, and reported early cohorts have not identified a recurring pattern of graft-derived tumors [3]. Nevertheless, most trials remain small and focused primarily on safety, while long-term tumor risk, durability, batch consistency and comparative effectiveness remain unresolved [3, 5]. By 2026, iPSC medicine has progressed from demonstrating technical feasibility to determining whether well-characterized products can deliver reproducible and clinically meaningful benefit in larger controlled studies [3, 12, 17].

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IMAGE FROM CANVA.COM

## Trends of Gene Therapy Clinical Trials

### Introduction

Q1 2026 marked a slower period for regulatory approvals across gene, cell, and RNA therapies, alongside a growing emphasis on evidence-based development and de-risking. As of 2026 Q1, 40 gene therapies, 37 RNA therapies, and 75 non-genetically modified cell therapies had received approval worldwide. For gene therapies and RNA therapies, no new approvals in Q1. As for non-genetically modified cell therapies, there were two new approvals in Japan: Sumitomo's raguneprocet for Parkinson's disease and Cuorips' ReHeart for heart failure. [1]

Across the cell, gene, and RNA therapy pipeline, 2132 gene therapies were in development, accounting for 50% of the total pipeline. CAR-T remained the leading technology, accounting for 52% of genetically modified cell therapies. Oncology and rare diseases remained major areas of gene therapy development. As for common indications, acute lymphocytic leukemia, systemic lupus erythematosus, and brain cancer are the top three among therapies with specified indications.[1]

### CRISPR (two 2026 clinical trials)

Against this backdrop, advances in liver-directed gene editing in 2026 illustrate the broader shift toward evidence-driven development and de-risking. The following two clinical trials published in 2026 used lipid nanoparticles (LNPs) for the systemic delivery of CRISPR-based gene-editing systems to the liver.

One representative example is the phase 1 trial of YOLT-101, an in vivo adenine base-editing investigational therapy for heterozygous familial hypercholesterolemia (HeFH). This trial aimed to develop a potentially one-time treatment that could reduce the need for repeated administration of therapies such as inclisiran, a PCSK9-targeting siRNA therapy which silences expression of PCSK9 in hepatocytes.

Via GalNAc-modified LNPs, high-precision adenine base editor (hpABE5) mRNA and sgRNA were delivered to hepatocytes. By doing so, the base-editing system targets PCSK9, disrupts normal PCSK9 mRNA splicing, and thereby reduces circulating PCSK9 and LDL-C levels. [2] Six participants received escalating doses (0.2, 0.4, 0.6 mg/kg) of YOLT-101. Five of the six participants experienced treatment-related adverse events (AEs), all of which were mild to moderate. Fever, myalgia, vomiting, and other infusion-related reactions were the most common AEs (83.3%); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations occurred in 50% of participants, and no grade 3 or higher-level AEs were reported. At week 24, the 0.6mg/kg group had a mean 74.4% reduction in PCSK9 level and a mean 52.3% reduction in LDL-C. For context, a previous study of inclisiran reported a 60.7% PCSK9 reduction and a 38.1% LDL-C reduction. In addition to these early efficacy signals, the study included preclinical off-target evaluations and a planned long-term follow-up, highlighting the integration of therapeutic innovation with systematic risk evaluation in gene-editing trials. [2]

A second example is a phase 3, double-blind, randomized, placebo-controlled trial published in The New England Journal of Medicine. Lonvoguran Ziclumeran (lonvo-z) is an investigational, single-dose, in vivo gene-editing therapy for hereditary angioedema. LNPs deliver *Streptococcus pyogenes* Cas9 mRNA and an sgRNA targeting KLKB1. After translation, Cas9 protein forms a complex with the sgRNA and is directed to the KLKB1 gene, which encodes prekallikrein, to inactivate it. Once KLKB1 is inactivated, prekallikrein and plasma kallikrein levels decrease, further reducing excessive bradykinin production and vascular permeability. [3]

A total of 80 patients from multiple countries were randomly assigned to lonvo-z (50mg) or placebo group at a 2:1 ratio and stratified by baseline attack rates of  $\leq 3$  or  $> 3$  attacks per month. Efficacy was evaluated by the monthly HAE attack rate from weeks 5 to 28 after infusion. The mean monthly attack rate was 0.26 attacks/month in the lonvo-z group compared with 2.10 attacks/month in the placebo group, corresponding to an 87% relative reduction ( $P < 0.001$ ). Long-term follow-up remains important to evaluate the risk of off-target editing. However, compared with the YOLT-101 phase 1 clinical trial, this randomized phase 3 trial provides higher-level clinical evidence that liver-directed in vivo gene editing has progressed to late-stage clinical validation. Together, these two trials demonstrate different stages of evidence generation in current gene-editing development. [3]

## AAV (two 2026 clinical trials)

Alongside CRISPR-based approaches, AAV gene therapy remains essential to clinical development, particularly for long-term gene replacement. One example is the phase 1 clinical trial of NGGT006. Like YOLT-101, which edits the PCSK9 gene to treat heterozygous familial hypercholesterolemia (HeFH), NGGT006 is also for familial hypercholesterolemia. However, NGGT006 is for homozygous familial hypercholesterolemia (HoFH), and it uses a recombinant AAV serotype 8-based vector to carry codon-optimized LDLR complementary DNA. To promote liver-specific expression, a human alpha 1-antitrypsin (hAAT) promoter was inserted. Restoring LDLR expression enhances hepatic uptake of LDL particles and lowers circulating LDL-C. [4]

In HoFH hamsters, a single dose of NGGT006 was injected at either a high ( $1.25 \times 10^{13}$  vg/kg) or a low ( $4.17 \times 10^{12}$  vg/kg) dose. At 28 weeks, LDL-C levels were reduced by 72% and 62% in the high- and low-dose groups, respectively. In rhesus monkeys, NGGT006 was also injected to evaluate the toxicology and immunogenicity. Both high ( $5 \times 10^{13}$  vg/kg) and low ( $1.5 \times 10^{13}$  vg/kg) dose groups achieved sustained liver transduction and dose-dependent human LDLR expression during the 10-week follow-up, with only transient ALT elevations and no adverse clinical observations or major organ abnormalities. [4]

Three patients received escalated doses ( $7.5 \times 10^{12}$ ,  $1.5 \times 10^{13}$ , or  $3 \times 10^{13}$  vg/kg) of NGGT006. Among them, the high-dose participant showed a marked decrease in LDL-C level: from 11.17 to 0.26 mmol/L and maintained a  $> 90\%$  reduction after week 6. The medium-dose participant showed a contrasting response: although there was a reduction at the beginning, the LDL-C level was 1.61 mmol/L higher than baseline after 52 weeks. The low-dose participant showed a modest response: the LDL-C level was 1.2 mmol/L lower than baseline after 52 weeks. The responses varied across participants, highlighting the uncertainty of dose-response relationships in this three-participant first-in-human study. All three patients had increased ALT/AST levels but no severe adverse event.

Although the relationship between treatment-induced anti-AAV8 neutralizing antibodies, adverse events, and therapeutic efficacy remained unclear in this small cohort, immune responses remain a major translational challenge because of the possibility of affecting the efficacy of therapy. Furthermore, patients with pre-existing AAV8 neutralizing antibodies were excluded unless antibody levels could be reduced to negative, which means the treatment eligibility may be limited. [4]

Another 2026 study, the phase 1–2 clinical trial of AAV9-GLB1, further illustrates both the therapeutic potential and immune challenges in AAV therapy. Type II GM1 gangliosidosis is caused by biallelic variants in GLB1, resulting in lysosomal  $\beta$ -galactosidase deficiency and abnormal GM1 ganglioside degradation. Impaired degradation of GM1 ganglioside leads to lysosomal substrate accumulation and progressive injury to the central nervous system. AAV9-GLB1 delivers a functional GLB1 gene to restore  $\beta$ -galactosidase activity and promote GM1 ganglioside degradation. [5]

During the trial, a single dose of AAV9-GLB1 was injected into twelve children with type II GM1 gangliosidosis through IV. The reported analysis included nine participants with at least two years of follow-up. Five participants received  $1.5 \times 10^{13}$  vg/kg and four received  $4.5 \times 10^{13}$  vg/kg. Over up to three years of follow-up, CSF  $\beta$ -galactosidase activity increased and GM1 ganglioside levels decreased. Functional outcomes were mixed: expressive communication and gross motor scores appeared stable, whereas fine motor and receptive communication scores declined. Most adverse events were mild to moderate, but liver-enzyme elevations occurred in all participants and one serious event of vomiting requiring hospitalization was attributed to the gene therapy. However, AAV9 activated anti-vector immune reactions in all participants and potentially limited the future readministration of the same vector. Different from NGGT006, which restores LDLR expression in hepatocytes, AAV9-GLB1 restores  $\beta$ -galactosidase activity and reduces GM1 ganglioside accumulation by delivering a functional GLB1 gene. [5]

Taken together, while immune responses, variable clinical efficacy, and patient eligibility remain major barriers to broader clinical application, these two studies show that AAV-based gene therapy continues to expand across distinct disease areas, from inherited metabolic disorders to progressive neurological diseases. [4,5]

## Conclusion

Despite its therapeutic potential, gene therapy remains associated with considerable clinical uncertainty. Both efficacy and safety require careful consideration. The 2026 ClFFREO trial provides an important negative example. Fordadistrogene movaparvovec is an investigational rAAV9-based gene therapy encoding a mini-dystrophin transgene protein for Duchenne muscular dystrophy. However, further clinical development of the therapy was discontinued because the trial failed to meet the primary efficacy endpoint and the overall benefit–risk profile was negative based on both efficacy and safety data. The outcome emphasized that a compelling biological rationale doesn't represent the success of translating into a meaningful clinical outcome. [6]

Taken together, clinical trials published in 2026 suggest gene therapy is transitioning from expansion to more evidence-driven and risk-aware development. Therefore, clinical validation, long-term safety monitoring, and systematic de-risking will be critical to future advancement.

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## 17<sup>TH</sup> ACTO ANNUAL MEETING

The 17th Annual Meeting of the Asian Cellular Therapy Organization (ACTO), held in collaboration with the Indonesian Stem Cell Association (ASPI).

Programme Highlights :

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- Scientific, regulatory, clinical, and public sessions
- Organization and networking meetings

More information:

<https://acto-hq.org/acto-2026-in-jakarta/>



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26–28 August 2026

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## 20 Years of iPSC Discovery: A Celebration and Vision for the Future

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## ISSCR - iPSC 20th Anniversary Symposium

The discovery of induced pluripotent stem cell (iPSC) technology has revolutionized biomedical research and regenerative medicine. To celebrate the 20th anniversary of this transformative breakthrough, the ISSCR is bringing together the global stem cell community in Kyoto, the birthplace of iPS cells, for a three-day symposium. This program will reflect on two decades of remarkable progress and explore the future of the field.

More information:

<https://www.isscr.org/upcoming-programs/2026-kyoto-international-symposium>

## ESGCT 33<sup>RD</sup> ANNUAL CONGRESS

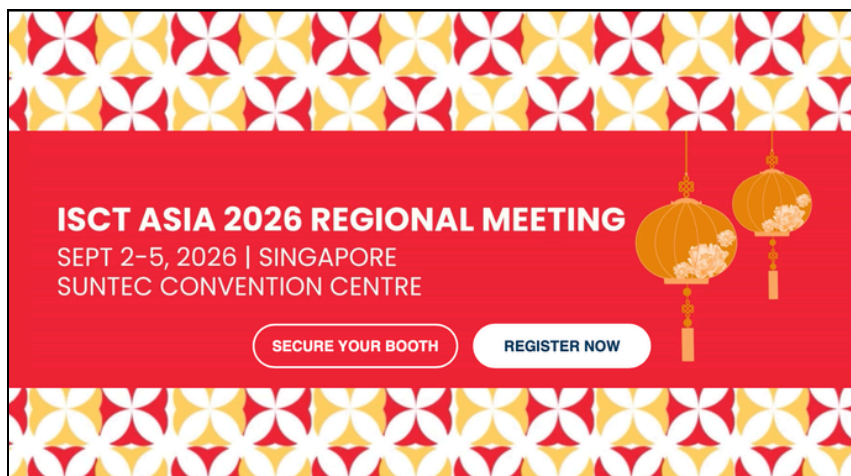
The ESGCT 33rd Annual Congress takes place in Hamburg, Germany, from 27-30 October 2026. The Congress is being held in collaboration with DG-GT.

The ESGCT Annual Congress brings together experts, researchers, and professionals in gene and cell therapy. The Congress is an invaluable platform for sharing the latest research, advancements and innovations in the field. Join us to connect, learn, and contribute.

More information:

<https://www.esgctcongress.com>





## ISCT ASIA 2026 REGIONAL MEETING

The International Society for Cell & Gene Therapy (ISCT) Asia 2026 Regional Meeting will be held on September 2-5, 2026, at the Suntec Singapore Convention & Exhibition Centre, Singapore. This premier event will bring together researchers, clinicians, industry leaders, and regulators to discuss the latest advances in cell and gene therapy.

More information:

<https://www.isctglobal.org/isctasia2026singapore/home-2026>

## APSEV 2026

This year's meeting will be held in conjunction with APSEV 2026, organized by the Asia Pacific Society for Extracellular Vesicles.

Building upon Japan's pioneering achievements in extracellular vesicle (EV) research from basic science to applied studies, we aim to send a strong message to the world about the future of EV research from Japan, as leading researchers across the Asia-Pacific region gather together. Accordingly, the joint conference theme is "Beyond Exosome."

More information:

[https://www.ace-enterprise.jp/apsev-jsev2026/en\\_index.html](https://www.ace-enterprise.jp/apsev-jsev2026/en_index.html)

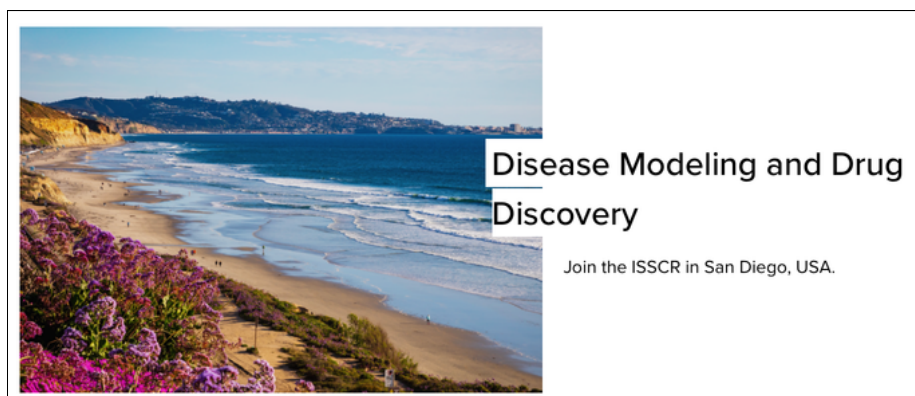


## ISSCR DISEASE MODELING AND DRUG DISCOVERY SYMPOSIUM 2026

Stem cell-based models are transforming disease understanding and accelerating drug discovery. This three-day symposium brings together global leaders from academia, industry, and the clinic to explore these transformative platforms. Sessions will feature advances in organoid systems that integrate multiple cell types, innovations in bioengineering, patient-derived tumor models, and AI-driven analytical approaches.

More information:

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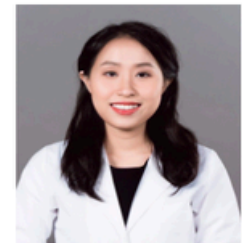
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