The ACTO Times

Asian Cellular Therapy Organization

Autumn Edition

India Spotlight
Extracelular Vesicles
CGT Contract Research, Manufacturing, and Testing

Greeting

ACTO Chairperson

Dear ACTO Members,

We are pleased to share the autumn edition of The ACTO Times. Founded in 2010 to support Asia's scientific community, ACTO was created by experts from across Asia as an accessible alternative to ISCT. Our first meeting, led by Dr. Yoichi Takaue in Miyazaki, Japan, brought together leaders from Taiwan, Singapore, Korea, Thailand, Iran, and China to create a platform suited to the unique needs of our region.

Since then, ACTO has held annual meetings across Asia, uniting academia, industry, and regulatory agencies to advance new therapies for patients. The ACTO Times, led by Editor-in-Chief Prof. Rita Yen-Hua Huang of Taipei Medical University, was approved at our recent meeting in Fukuoka and will be published quarterly. Each edition will feature insights from across our community, including updates from regulatory and industry committees.

Your input is invaluable as we strive to make The ACTO Times a key resource for our members. Thank you for your support and contributions.

Warm regards,

Akihiro Shimosaka

Editorial Greeting

The ACTO Times Editor-in-Chief

Dear Readers and Contributors,

I am thrilled to present the Autumn Edition, which features a spotlight on India and includes a special report on exosome development—covering its pros and cons—as well as advancements and industry updates related to CGT contract research, manufacturing, and testing.

The global development of CGT is progressing rapidly. As of October 2024, there are 86 CGT (cell and gene therapy) products approved for market worldwide, including 30 gene products and 21 allogeneic cell products. Currently, there are 2,900 regenerative medicine companies globally, with 944 having entered clinical development.

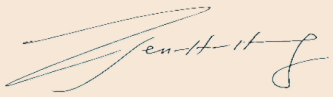
There are a total of 1,900 clinical trials related to CGT, of which 98 have entered Phase III, primarily focusing on gene and cell therapy products. In terms of global clinical trials and regenerative medicine companies, Asia is the fastest-growing region for CGT.

With heartfelt enthusiasm for Asia, The ACTO Times serves as a platform for the global advancement of CGT, with a particular focus on the Asia-Pacific region. Our goal is to facilitate the exchange of culture and knowledge while fostering global connections in education, regulation, clinical practice, and industry.

In recent months of 2024, The ACTO Times has received invaluable recognition for the Spring and Summer Editions. We explored the history of ACTO and highlighted recent advancements in CGT in Asia, including preclinical research, clinical trial updates, and industry developments in immune cell therapy (CAR-T and immune cells) and stem cell therapy (MSC, HSC), as well as CGT regulations in various Asian regions.

Thank you for being a part of ACTO and The ACTO Times. I sincerely invite you to actively engage with The ACTO Times, and I look forward to our collaboration in CGT therapy in Asia and beyond.

Sincerely,



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CONTENTS

HISTORY OF HEMATOPOIETIC GROWTH FACTORS FROM DISCOVERY TO CLINIC: LESSONS FROM AKIHIRO SHIMOSAKA

Summarized by Joseph Wangisani Chisaka

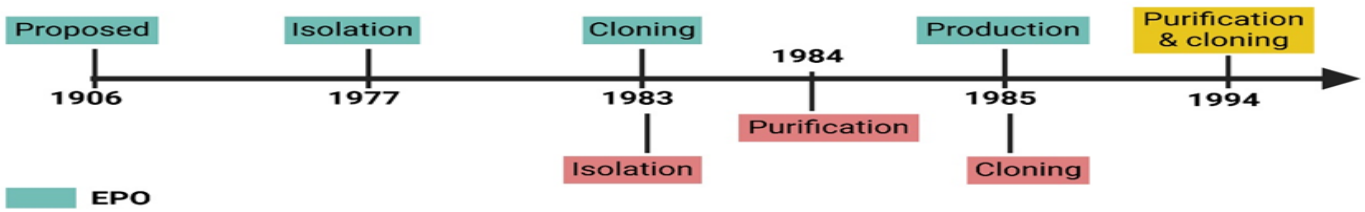
Background

All blood cells are derived from hematopoietic stem cells (HSCs) which originally are derived from Embryonic stem cells (ESCs). Various growth factors have been speculated as being responsible for lineage specific proliferation and differentiation of stem cells to mature cells. By the late 1980's, some essential hematopoietic growth factors (HGFs) common among animals, such as Erythropoietin (EPO), Granulocyte-Colony Stimulating Factor (G-CSF), Thrombopoietin (TPO) and Stem cell Factor (SCF) were purified, responsible genes for each factor cloned and reproduced by recombinant technology for clinical use. These factors have been in clinical use since then up to date, they are essential to animal life and their amino acid sequences are well preserved in various animals. There is similarity of amino acid sequences of the molecules among animal species such that human molecules are effective in other animals.

EPO was the first HGF to be isolated in 1977. Although EPO's presence was first reported in 1906 and its production by the kidneys reported in 1950, it took another 27 years to finally isolate and purify it. Eugene Gold Wasser and Takaji Miyake at Chicago University, using urine from aplastic anemia patient in Kumamoto, Japan, purified EPO by labor intensive animal in vivo assays. After the introduction of gas-phase sequencing, Por Lai sequenced amino acid in 1982, then EPO gene was finally cloned in 1983 by Fu-Kuen Lin, Amgen. EPO contains a large sugar moiety in its structure which plays an important role for its in-vivo activity. Its production method was developed by Joan Egrie, Jeffrey Browne and Steve Elliot. Later, Kirin Brewery developed large scale production system which made it possible for further studies and clinical application. EPO needs to be produced in mammalian cell. As such, CHO cell was used for drug production, which needed new regulations. New standard for the use of CHO cells were defined in first in the USA and Japan, followed by Europe and other countries.

G-CSF is one of the early cytokines to be identified and rapidly entered into clinical trials. In the 1960's, two independent groups of Ray Bradley and Don Metcalf at the University of Melbourne, Australia, and Yasuo Ichikawa

Isolation of HGFs



Time periods in the identification erythropoietin (EPO), Granulocyte-Colony Stimulating Factor (G-CSF) and Thrombopoietin (TPO)

and Leo Sachs at the Weizmann Institute, Israel, developed colony assays in semi-solid culture to test the effects of colony stimulating factors in hematopoietic cell differentiation pass way. In 1983, Nicos Nicola, Water-Elaiza Hall Institute, Melbourne, isolated mouse G-CSF from endotoxin treated mice, Karl Welte purified Human G-CSF, Memorial Sloan Kettering Cancer Center, from conditioned media of bladder carcinoma cell line 5637 in 1985, and Larry Souza cloned its gene in 1985. G-CSF produced by E. coli. E.coli produced G-CSF is aggregated form which has no activity. However, it can be solubilized for purification and folded into active form again by refolding technology.

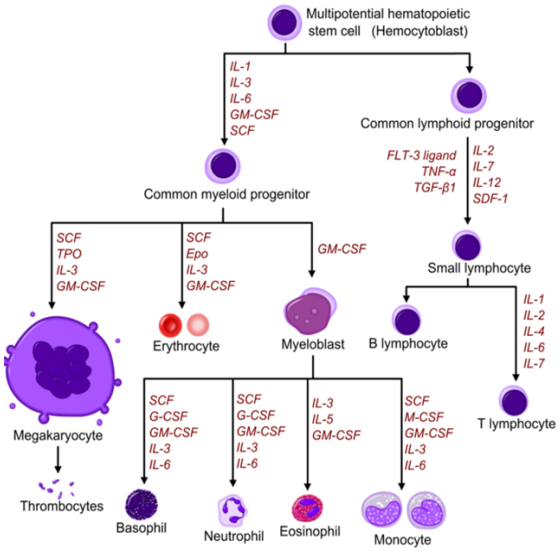
TPO was purified by five research groups (Kirin, University of Washington/Zymogenetics, Genentech, Amgen and MIT), and human gene was cloned in 1994. Kirin purified TPO using in-vivo assay while other groups speculated that c-mpl would be the receptor for TPO after the identification of the putative TPO receptor in 1991.

Clinical application of HGFs

EPO is widely used in the management of anemia from different causes like renal failure where the kidneys fail to produce it. EPO has been demonstrated to improve both survival and quality of life in these patients. EPO is also used in autologous blood donation, which is considered the safest blood resource in transfusion. Since glycosylation is essential for EPO in-vivo bioactivity, the synthwwwwetic EPO (Aranesp) is from a genetic modification on the original EPO to provide more glycosylation to prolong its half-life. Aranesp is currently widely used as a synthetic EPO.

G-CSF discovery helped revolutionize the delivery of anti-cancer therapy. Although originally intended for neutrophil production in neutropenic patients (especially chemotherapy induced), its added advantage of being able to mobilize HSCs from the bone marrow into the peripheral blood which made possible to use peripheral HSC for hematopoietic stem cells transplantation both autologous and allogeneic,

TPO regulates platelet production by targeting thrombopoietin receptor (TPO-R). TPO-R agonists (TPO-RAs) are currently used to treat thrombocytopenia in chronic immune thrombocytopenia (ITP), severe aplastic anemia (SAA), chronic liver disease (CLD) patients undergoing surgery, and hepatitis C virus (HCV) infection. Various studies have shown that TPO-RA treated patients had less bleeding, needed fewer platelet transfusion, reduced/eliminated corticosteroid use and overall demonstrated improved quality of life.



Hematopoietic growth factors involved at different cell differentiation stages from the hematopoietic stem cell (https://qkine.com/hematopoietic-stem-cell-research/)

Conclusion

Essential HGFs discovery remarkably impacted the clinical world. HGFs are lineage specific; EPO for erythrocytes, G-CSF for granulocytes/neutrophils and TPO for megakaryocytes/platelets. Essential HGF activity is not species specific; human HGFs are active in animals. HGFs further possess stem cell mobilization activity in the descending order from G-CSF, TPO, SCF to EPO. Used within appropriately recommended amounts, minimal clinical side effects have been reported on HGFs.

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Akihiro Sh

Chairperson: *Asian Ce*

Director: *Research Found*

The speech was delivered

Today, situation around us is very similar to the situation around 2010 related to unproven cellular therapy when we published appeal.

Exosome will be very useful tool for the next generation therapy however exosome safety and suggesting efficacy information must be disclosed. There is no specific regulation directly control exosome yet but general rule, any material administered in human must have safety data and efficacy suggesting data. In some country, if doctor and patient agree, any therapy can be given to patient. However, doctor must disclose every information related to safety and expected efficacy and this therapy must be approved by ethics committee. So even there is no specific regulation which control exosome, we can control based on already existing regulation. Even cosmetic field, it must have safety information and expected efficacy information.

Our organization, ACTO is responsible for the development of new therapy needed for the patient treatment under collaboration among academy, industry and regulatory agency. We need to share all the information among three players. I would like to share our experiences with you and take action for next step.

We need to re-consider current practice related to cellular therapy.

Cellular therapy became very important therapy for the patient treatment. However, regulation for the autologous cellular therapy is still not well regulated yet. CAR-T therapy is regulated like ‘drug’ based on marketing authorization system though processed CAR-T cell can be used only for the patient who provided cells for processing. There are several issues among CAR-T cell therapy today.

1. CAR-T cell technology was developed as conditioning regimen prior to allogeneic hematopoietic stem cell transplantation (HSCT) to minimize remaining tumor cells at the time of transplantation. To minimize remaining malignant cells,

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the best is no detectable malignant cell, is the key for the good outcome of allogenic HSCT. For this purpose, CAR-T therapy was developed. Then even using virus gene for gene construct transfection and targeting CD19 antigen which is also expressed on normal cells, were OK because after CAR-T therapy, conditioning treatment for allo HSCT will kill all the CAR-T cells. When company involved in the development of CAR-T therapy, they want to develop CAR-T therapy as single therapy, not combining allo HSCT. Then there are issues remaining, risk of virus gene and keep killing CD19 expressing normal B cells. Recently, there are report on the secondary T-Cell malignancies after CAR-T therapy. There are two virus genes used in CAR-T therapy today, retro and lenti virus. T-cell malignancies are reported both after retro and lenti virus CAR-T therapy. There are questions related to the construct of gene, either CD28 or 4.1 BB. Which is better? Japanese experiences showed CD28 construct is more potent than 4.1 BB construct. Cytokine release syndrome (CRS) after CAR-T therapy, 4.1 BB construct may have less CRS. Some group reported that CAR-T treatment followed by Allo HSCT has far better survival than CAT-T therapy alone. Pricing is another issue among CAR-T therapy. Novartis introduced CAR-T technology from University of Pennsylvania though U. Pen introduced CAR-T technology from St. Jude Children Hospital. St. Jude licensed its technology to Juno. Novartis infringed Juno patent right. Then Novartis pay huge amount of downpayment and promised royalty payment. Which made Novartis to charge huge price on CAR-T therapy. Other companies just followed Novartis price.

2. To activate antigen specific immune response, dendritic cell (DC) is the better method. Immune reaction is comprehensive system, not just T-cell but NK, NKT, macrophage and neutrophil are involved. To transfer immune response signal is created by DC. We can use DC derived exosome for immune signal transfer to all immune cells. We can load antigen directly on DC derived exosome. Can load multiple antigens at the same time. Then we can expect immune response by all immune related cells, not just T-cell. Then this can give more potent immune response against target. We studied DC derived exosome for the cancer treatment and can induce immune response.
3. Multiple myeloma can be treated by high dose CT followed by autologous HSCT. Recently US FDA approved autologous HSCT for multiple myeloma treatment. This is important step for regulatory stand point. We need system to approve 'therapy' which authorize therapy officially and can be reimbursed by public

insurance. Treatment authorization may be granted hospital by hospital base. We have already studied high dose CT followed by autologous HSCT combined with DC therapy. Combined with DC therapy immunized by patient idiotype antigen showed better 5-year survival. But at that time there is no system to approve autologous therapy. There is no commercial product, because DC and antigen is obtained from patient. No company showed any interest though it did work. Today, still company is not interested in such therapy but for patient, it is important. It is time for the hospital to develop such unique therapy for the patient treatment. There will be business opportunity for the company to provide service to the hospital.

4. CD34+ cell regenerative therapy in USA and Europe showed different outcome. In USA study used Baxter developed Isolex system and Europe used Miltenyi CliniMACS system. Then outcome in Europe was good but outcome in USA was disappointing. This was due to different CD34+ cell separation system. Isolex system gave damage on CD34+ cells. Though autologous CD34+ cell for regenerative therapy dose work but again there is no commercial product for distribution. We need system to authorize such autologous cellular therapy.

Based on such experiences, we proposed new regulation to be introduced which can authorize autologous cellular therapy and it was accepted by Japanese and Taiwan agency. It became effective 2014 in Japan and 2024 in Taiwan.
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Based on such experiences, we proposed new regulation to be introduced which can authorize autologous cellular therapy and it was accepted by Japanese and Taiwan agency. It became effective 2014 in Japan and 2024 in Taiwan.

EXPLORING THE POTENTIAL OF LYOPHILIZED MSC-DERIVED EXTRACELLULAR VESICLES IN ALLEVIATING ARD IN MASS CASUALTY SCENARIOS

Sai Kiang Lim, PhD

Research Director, Paracrine Therapeutics

The speech was delivered at the Symposium on Cell Derivatives and Drug Development at National Taiwan University, Taipei

Summarized by Vijetha Karen Kitchley
Taipei Medical University

Acute Radiation Syndrome (ARS) is a rare and complex condition resulting from exposure to high doses of radiation over a short period. The disorder presents a significant medical challenge, with limited therapeutic options available. Developing effective treatments for ARS is of critical importance, particularly in the context of potential mass casualty events caused by nuclear power plant accidents, terrorism, or nuclear war.

The pathology of ARS varies based on the radiation dose and tissues affected, primarily targeting rapidly dividing cells in the hematopoietic system (U-ARS), the gastrointestinal tract (GI-ARS), and the nervous and cardiovascular systems (CNS-ARS). ARS is primarily characterized by DNA damage at both the physical and chemical levels.

Mesenchymal stem cells (MSCs) have shown promise in alleviating ARS, as evidenced in clinical trials and animal models (Fukumoto 2016). However, their use in large-scale disasters presents several challenges:

1. Feasibility of Stockpiling MSCs: Creating a stockpile of MSCs is essential for preparedness in case of a major catastrophe. However, MSCs are live cells with a finite lifespan and limited capacity for expansion, restricting the potential size of such a stockpile. In addition, MSCs require cold chain storage, complicating their availability during emergencies and potentially delaying their timely delivery to patients in need.

2. Mechanism of Action: The in vivo behavior of MSCs is unpredictable due to their responsiveness to the surrounding microenvironment, especially under the dynamic conditions of tissue damage. This makes it challenging to precisely understand how MSCs mitigate the effects of ARS.

Concerns from regulatory bodies like the U.S. Food and Drug Administration (FDA) highlight the challenges in using MSCs clinically, particularly regarding the limited lifespan of primary cells and difficulties in defining critical quality attributes.

Importantly, research increasingly suggests that MSCs exert their therapeutic effects primarily through secretions rather than differentiation. This has led to the exploration of non-living extracellular vesicles (EVs), 50-200 nm particles secreted by MSCs, as potential therapeutic alternatives (Witwer, Van Balkom et al. 2019). While EVs could address several issues associated with live MSCs, challenges remain, particu-

larly concerning the source of EV-producing cells.

Addressing the Challenges with MSC-derived EVs:

- Cell Source: Primary MSCs used to produce EVs face the same supply constraints due to their limited lifespan. However, since MSCs intended for EV production are not administered to patients, they can be immortalized and cloned to create monoclonal cell lines for large-scale EV production. Immortalized cell lines are commonly used in the production of biologics and offer a stable, renewable source of cells for producing MSC-derived EVs (Chen, Arslan et al. 2011).
- Storage and Distribution: To overcome the issues related to cold chain logistics, MSC-derived EVs can be lyophilized (freeze-dried). This allows for easier storage and distribution without the need for cold storage.

In a notable study, Radia et al. demonstrated the potential of lyophilized MSC-derived extracellular vesicles in alleviating radiation-induced gastrointestinal toxicity(Accarie, l'Homme et al. 2020). The study showed that these EVs promoted epithelial repair and regeneration in mice, preserving the structural integrity of the intestinal epithelium following radiation exposure.

This research suggests that lyophilized MSC-derived EVs from immortalized MSCs could be a viable solution for mitigating GI-ARS. They can be produced in unlimited quantities, stockpiled for major catastrophes, and stored without the need for cold chain logistics. This approach offers an infinite supply of therapeutic EVs, addressing many of the current limitations associated with MSC therapies for ARS.

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UPDATES ON CLINICAL TRIALS:

Josephine Diony Nanda, M.D., Ph.D.

Department of Parasitology, Faculty of Medicine, Public Health and Nursing,

Univeristas Gadjah Mada, Indonesia

Recent advancements in regenerative medicine have highlighted the potential of exosome and secretome therapies in treating various diseases. Exosomes, small extracellular vesicles derived from cells, and secretomes, the collection of bioactive molecules secreted by cells, have shown promising results in preclinical studies. This report provides an overview of the latest updates in clinical trials involving exosome and secretome therapies, categorized by disease type, taken from www.clinicaltrial.gov on September 27, 2024.

Exosome-Based Clinical Trials

Exosome-based therapies have been explored for a wide range of conditions. Overall, 53 trials were reported on www.clinicaltrial.gov for the use of exosomes in those various conditions mentioned above. However, only five of them reported that they had obtained results, and the others disclosed no results obtained. According to recent data, exosome clinical trials are distributed across several disease categories.

In the realm of cancer and tumors, there have been 21 trials investigating the use of exosomes. This significant number underscores the potential of exosome-based treatments in oncology, a field in urgent need of innovative therapeutic strategies.

Degenerative diseases have also been a major focus, with nine clinical trials dedicated to exploring the efficacy of exosome therapies. These conditions, often characterized by the gradual deterioration of cells and tissues, could greatly benefit from the regenerative properties of exosomes. In addition, one trial has been conducted for genetic and congenital disorders, highlighting the versatility of exosome therapy in addressing a variety of genetic anomalies. Healthy individuals have participated in eight clinical trials, aiming to assess the safety and potential preventive benefits of exosome treatments. This inclusion emphasizes the importance of understanding how these therapies interact with non-diseased bodies, which could pave the way for preventive applications. Infection-related trials have also seen significant activity, with eight studies investigating how exosomes can be harnessed to combat various infections. Lastly, one trial has focused on wounds and injuries, exploring the potential of exosome therapy in accelerating the healing process and improving outcomes in tissue repair.

Secretome-Based Clinical Trials

Similarly, secretome-based therapies have been investigated for various conditions, including autoimmune diseases (3 trials), dermatology (2 trials), degenerative diseases (1 trial), healthy individuals (1 trial), infections (2 trials), and wounds and injuries (4 trials).

The distribution of clinical trials indicates a strong focus on autoimmune, cancer, degenerative diseases, and infections for both exosome and secretome therapies, with some others focusing on wounds and injury and physiology in healthy individuals. This suggests that researchers are prioritizing conditions where the regenerative and immunomodulatory properties of exosomes and secretomes can have significant therapeutic impacts. The inclusion of healthy individuals in these trials also highlights the potential for preventive applications and the importance of understanding the safety and efficacy of these therapies in non-disease contexts.

Exosome and secretome therapies are emerging as promising approaches in regenerative medicine, with ongoing clinical trials targeting a diverse range of conditions. Continued research and development in this field are essential to fully realize the therapeutic potential of these innovative treatments. The report on the study with obtained results were summarized on the table below. Meanwhile, for the full table of both

EXOSOME AND SECRETOME

exosome and secretome clinical study can be downloaded on the link as follows https://docs.google.com/spreadsheets/d/1woD5Ar3yqfTHrs0FCRPwt2-o6zCWxj4l/edit?usp=sharing&ouid=118314909291177835856&rtpof=true&sd=true.

NCT Number	Topic	Trial Subject	Condition(s)	Phase	Study Title	Brief Summary
NCT04500769	Production	Healthy	Metabolism	NA	Training Induced Muscle Exosome Release	The primary objective of this study is to quantify miR-1 release from muscle in extra-cellular vesicles following an acute resistance exercise bout and potential delivery to subcutaneous adipose tissue in young healthy and obese adults.
NCT04313647	Safety	Healthy	Healthy	Phase 1	A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes In Healthy Volunteers	This clinical study will be performed to evaluate the safety and tolerance of aerosol inhalation of the exosomes derived from allogenic adipose mesenchymal stem cells (MSCs-Exo) in healthy volunteers.
NCT04491240	Safety	Infection	COVID-19	Phase 1|2	Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia.	This trial will record the number of participants with non-serious and serious adverse events during inhalation procedure for 10 days and any adverse events occur during all trial, 30 days after clinic discharge.
NCT03109873	Treatment	Cancer, tumor	Larynx|Lip|Oral Cavity|Pharynx	Early phase 1	Metformin Hydrochloride in Affecting Cytokines and Exosomes in Patients With Head and Neck Cancer	This pilot clinical trial studies how well metformin hydrochloride works in affecting cytokines and exosomes in patients with head and neck cancer. Metformin hydrochloride may reduce the metabolic activity of cancer cells and of surrounding supportive tissues.
NCT04493242	Treatment	Infection	COVID-19|ARDS	Phase 2	Extracellular Vesicle Infusion Treatment for COVID-19 Associated ARDS	To evaluate the safety and efficacy of intravenous administration of bone marrow derived extracellular vesicles, ExoFlo, versus placebo as treatment for moderate-to-severe Acute Respiratory Distress Syndrome (ARDS) in patients with severe COVID-19.

ADVANCEMENTS AND REG
AND GENE THERA

Navigating the Evolving Landscape of CGTPs:

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

Globally, basic and clinical research and development in cell and gene therapy products (CGTPs) are rising at a rapid pace. In the last few decades, India has also witnessed remarkable progress in this field due to a large number of rare genetic disorders and unmet medical needs. The scientific advances in CGTPs demonstrate potential for transforming the health of the nation by providing therapeutic options for many unmet medical needs.

Currently, India has 11 ongoing gene therapy clinical trials, five cell-based products with market authorization, and many more in the pipeline. The advancements in CGTP technologies have created a dilemma in the regulatory framework, which is traditionally defined to regulate pharmaceutical drug molecules. Worldwide, regulators face two major challenges: defining the framework to regulate CGTPs and curtailing the commercial use of cell-based products whose safety and efficacy are yet to be established.

The Indian regulator, the Central Drugs Standard Control Organization (CDSCO), under the Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare (MoHFW), Government of India, is responsible for implementing the Drugs and Cosmetics Act, 1940, and its amendments. Under this Act, CDSCO, headed by the Drug Controller General of India (DCGI), is responsible for drug approval, the conduct of clinical trials, establishing drug standards, controlling the quality of imported drugs, and coordinating activities of State Drug Control Organizations by providing expert advice to ensure uniform enforcement of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules (NDCTR) 2019. These rules also oversee market authorization and the import-export of advanced therapeutic products, in-

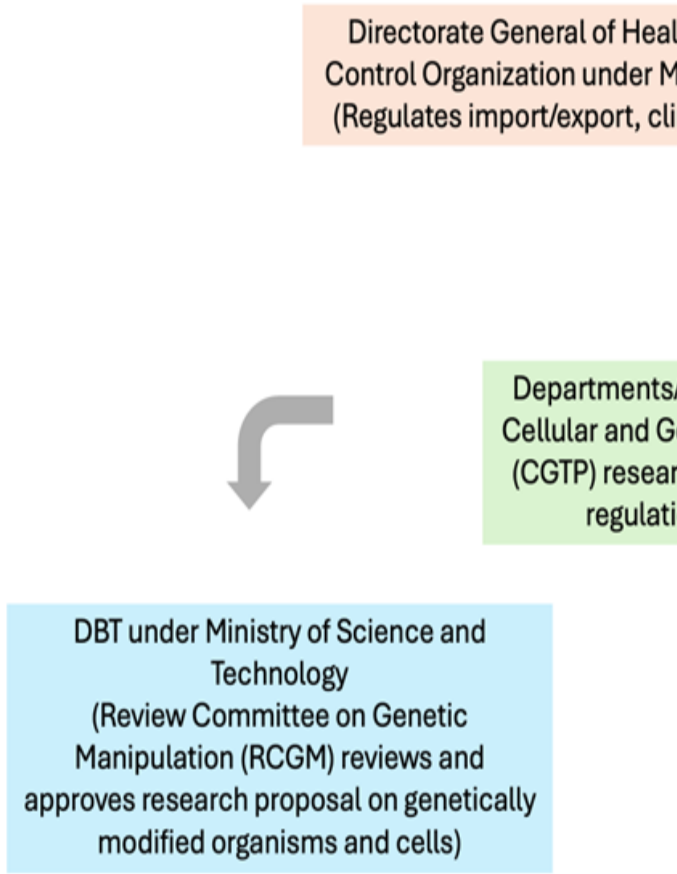


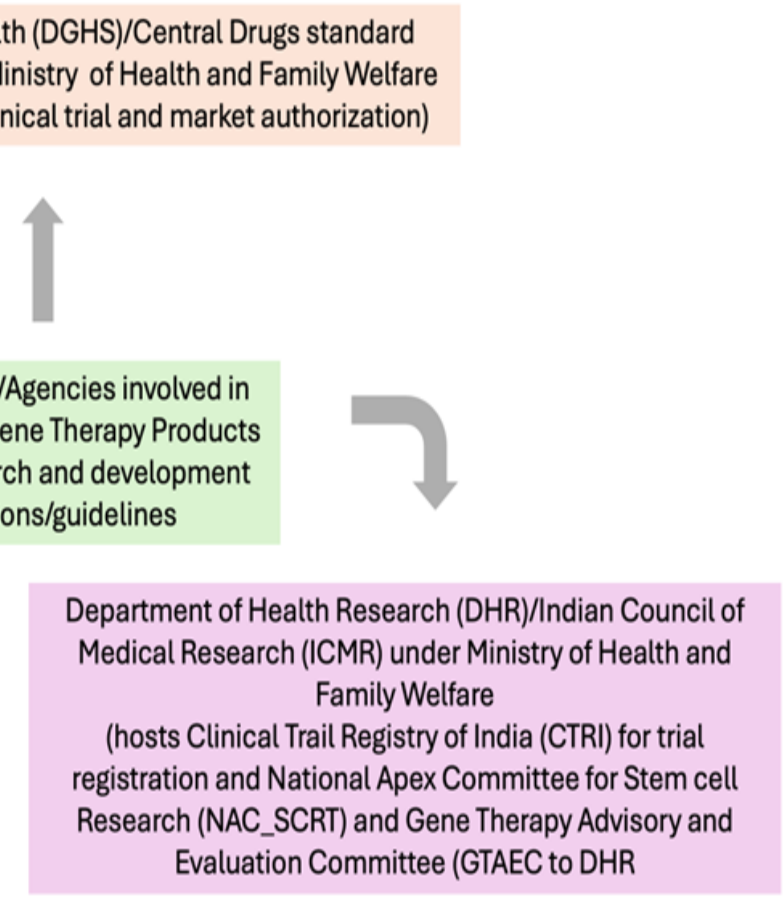
Fig. 1 Major Government agencies involved
of C

ULATORY CHALLENGES IN CELL PY PRODUCTS IN INDIA

: Opportunities for Innovation and Ethical Oversight

cluding CGTPs. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC).

Research on genetically engineered (GE) organisms or cells under the Environment (Protection) Act, 1986, is regulated by the Review Committee on Genetic Manipulation (RCGM) under the Department of Biotechnology (DBT). Additionally, the Indian Council of Medical Research (ICMR), a century-old apex body in India for the formulation, coordination, and promotion of biomedical research, has contributed to the field of CGTP through its guidelines (Figure 1).



in overseeing the clinical research and development GTP in India

Regulatory Framework for CGTP

The NDCTR 2019, under the Drugs and Cosmetics Act, 1940, governs new drugs, clinical trials, investigational drugs, bioequivalence and bioavailability studies, and ethics committees. In 2022, the NDCTR was amended to include "cell or stem cell-derived products" instead of just "stem cell-derived products." Regulations for genetically engineered (GE) organisms, hazardous microorganisms, and related products fall under the Rules, 1989, notified by the Ministry of Environment. Gene therapy products must comply with these regulations.

Umbilical cord blood (UCB), a source of stem cells, is regulated by the CDSCO, with specific guidelines for banking and storage outlined in a 2011 amendment. Research on stem cell therapies follows the National Guidelines for Stem Cell Research (NGSCR-2017), while gene therapy products are guided by the 2019 guidelines. The ICMR released the National Guidelines for Hematological Cell Transplantation (2021) and a report on the status of stem cell therapy to clarify proven versus unproven therapies. Ethical guidelines for biomedical research involving humans are also in place, all accessible on government websites.

Approval Process for CGTP in India

Entities intending to collect, isolate, store, and regulate clinical trials and the profitable use of CGTP must submit applications to the CDSCO through the Suraksha Gunvatta Avun Maanakta online portal. According to guidelines issued by the ICMR, in addition to CDSCO approval, the following approvals are also required:

- Clinical trials using cell- or stem cell-derived products must have prior approval from the Indian Council of Stem

Cell Research (ICSCR) and an Institutional Ethics Committee (IEC).

- Clinical trials using gene therapy products (GTP) must have prior approval from the RCGM as well as the IEC and should have been reviewed by the Gene Therapy Advisory and Evaluation Committee (GTAEC).

Challenges Ahead and the Way Forward

There is a global surge in the research and development of CGTP products, and India is also catching up. India has established guidelines for stem cell and gene therapy research over the past decade. To navigate the evolving landscape of CGTP and address emerging scientific and ethical challenges, India has set up multidisciplinary committees. However, significant regulatory gaps persist. Several critical questions remain unanswered regarding the regulation of CGTP in India:

- The definitions for "stem cell-derived products" are vague, potentially enabling unethical practices without sufficient evidence of safety and efficacy. The rules also lack clarity on what constitutes gene therapy products (GTP).
- Regulatory mechanisms do not address minimally manipulated cells or the non-homologous use of hematopoietic stem cells for various applications, including cosmetic procedures and bone healing.
- The NDCTR 2019 allows academic clinical trials for already approved drugs used in new ways, but CGTPs, being inherently new, should not be exempt from additional regulatory scrutiny and oversight.
- Current guidelines on umbilical cord blood (UCB) banking fail to provide detailed regulatory requirements covering the entire process from collection to storage, including checks on cell viability and quality control.

Addressing these gaps is essential for ensuring patient safety and ethical research practices in the rapidly evolving field of CGTP. To enhance regulatory clarity and ensure patient safety, there is a pressing need for harmonization of existing guidelines with international standards, particularly regarding definitions and oversight of CGTP. Regulatory frameworks should include rigorous evaluations of novel therapies and establish clear pathways for clinical trials. By reforming these mechanisms, India can foster an environment conducive to ethical research and innovation, ultimately positioning itself as a leader in global health advancements while safeguarding patient welfare.

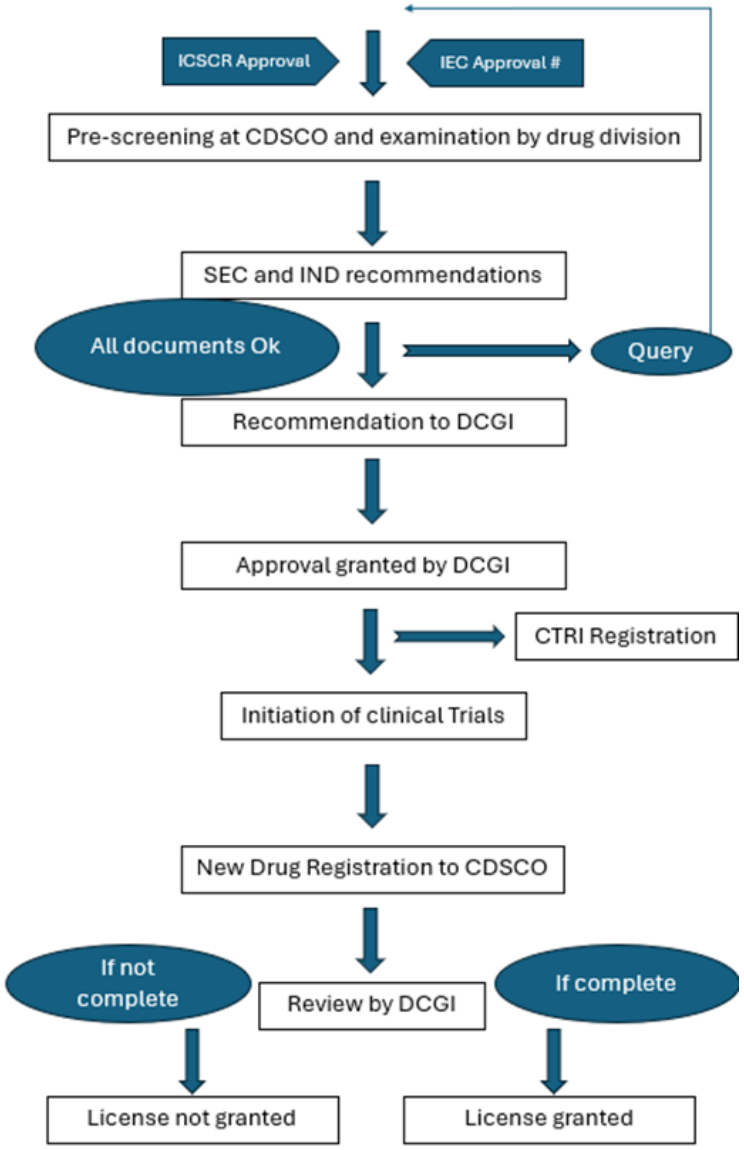


Fig. 2 Flowchart depicting the approval process of CGTP.

(# IBSC and RCGM approvals are required for GTP)

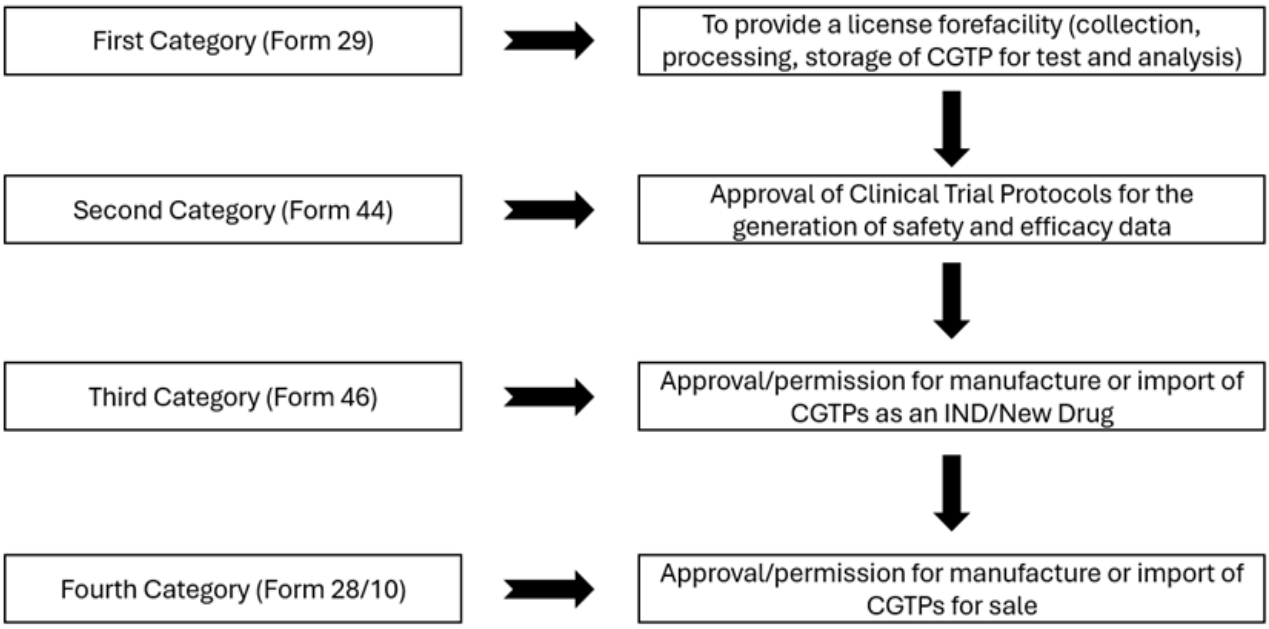


Fig. 3 Categories of approvals issued by CDSCO

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CURRENT ADVANCES AND UPDATES IN INDIA'S CGT: CLINICAL TRIALS AND APPROVED PRODUCTS

An Overview of Recent Developments, Regulatory Reforms, and Market-Approved CGT Products

Vivienne Johanna Kitchley
M.Sc. Clinical Research, Indian Institute of Clinical Research, Mumbai

On September 25, 2024, the WHO issued guidelines for designing scientifically sound and equitable clinical trials. These guidelines aim to ensure inclusion, comfort, and efficiency in clinical research. They seek to bridge the gap in the quality and quantity of clinical trials between high-income countries (HIC) and low- and middle-income countries (LMIC), encourage the inclusion of pregnant women and children in studies, and emphasize the importance of "patient, participant, and community engagement" in organizing clinical trials. The WHO has identified four key pillars for a sustainable and robust national clinical research ecosystem: national clinical research governance, funding and policy frameworks, clinical research infrastructure, ethical oversight, and regulatory systems.

The Indian government has established new standard operating procedures (SOPs) for Clinical Research Organizations (CROs) in the country. The New Drugs and Clinical Trials (Amendment) Rules, 2022, define CROs' roles, responsibilities, and liabilities. These new rules will take effect on April 1, 2025. The Central Licensing Authority of India will approve registration applications submitted by CROs to conduct clinical trials, bioavailability, or bioequivalence studies, valid for five years.

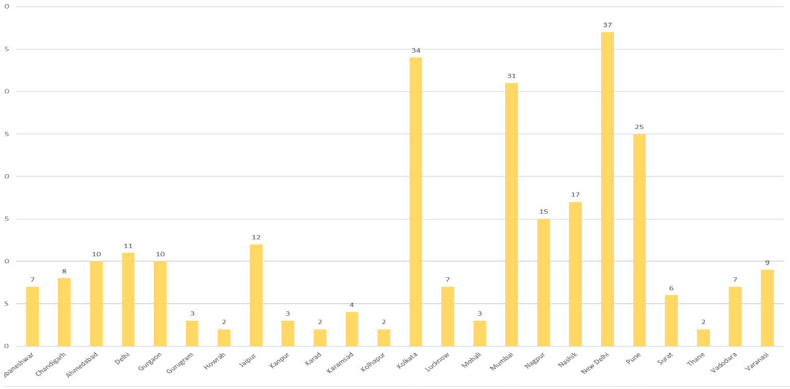

Figure 1: Graphical representation of cities having multiple trial site locations in North India

Clinical Trial History in India

India has emerged as a global hub for clinical trials over the past decade. Several factors have contributed to this rapid growth, including the Indian government's adoption of a 'product patent regime', the availability of a large patient pool, a vast number of qualified English-speaking medical professionals, cost advantages, an ethnically and age-diverse population, state-of-the-art facilities, and the IT revolution of 1990. The IT revolution facilitated the transition from paper-based systems to electronic clinical data management, streamlining processes and accelerating clinical research.
Multinational companies were attracted to conduct trials in India due to the presence of an illiterate and poverty-stricken population, a 'broken' healthcare system, and favorable regu-

No.	Name of Drug	Description and Indication	Year of Approval
1.	ReliNethra® (Autologous bioengineered composite limbal epithelial graft)	Epithelial graft for treating Unilateral Limbal Stem Cell Deficiency.	2008
2.	Stempeucell® (Adult Human Bone Marrow derived, cultured, pooled Allogenic Mesenchymal Stromal Cells)	Critical Limb Ischemia due to Buerger's Disease, Atherosclerotic Peripheral arterial disease, and Grade II or III Osteoarthritis	2016
3.	Trichosera® (Hair Serum prepared from the bioactive medium of mesenchymal stromal cells)	Bioactive Hair Serum	2016
4.	Cutisera® (Serum contains bioactive factors secreted from mesenchymal stromal cells)	Bioactive Skin Cream for moisturizing and brightening	2016
5.	Perioptisera® (Serum prepared from the bio-active medium of stem cells)	Undereye cream for dark circles and hydration	2016
6.	Cartigrow™ Chondron (Autologous Adult Live Cultured Chondrocytes in DMEM suspension for implantation)	Articular Cartilage Defects	2017
7.	Ossgrow™ (Autologous Adult Live Cultured osteoblasts in DMEM suspension for implantation (OSSRON))	Avascular Neurosis of Hip	2017
8.	Apceden® (Dendritic cell immunotherapy product)	Prostate, Ovarian, Colorectal, and Non-small cell Lung Cancer	2017
9.	DermACELL® (Decellularized Dermis)	Skin graft for Diabetic foot ulcer, Venous leg ulcer, Dehisced surgical wounds, and Traumatic Burns	2017
10.	UreGrow® (Autologous Adult live cultured Buccal Epithelial Cells)	Bulbar Urethral Stricture	2019
11.	NexCAR19™ (Autologous HCAR19 (2nd generation AntiCD19-41BBCD3ζ chimeric antigen receptor T-cell therapy))	Relapsed or Refractory B Cell Lymphomas Relapsed or Refractory B-Acute Lymphoblastic leukemia	2023
12.	IMN 003A (IMN-003A cells/anti-CD 19 CAR-T cells)	Relapsed / refractory B-NHL in Patients aged greater than 18	N/A

Table 1: All CGTs authorized for marketing in India as of October 2024

lations. These companies easily obtained trial approvals, recruited participants, and exploited the vulnerable population. The lack of proper regulation and the perception of doctors as gods contributed to the exploitation of participants, who often received inadequate compensation and provided uninformed consent.

Between 1999 and 2009, India witnessed several controversies related to clinical trials, including the Indore controversy (2004-2010, 35 deaths), the Bhopal controversy (since 2004, 14 deaths), the Cervical Cancer Screening Trial (1998-2011, 254 deaths), and the HPV Vaccine Trial (2009, 5 deaths). In 2010, the Supreme Court of India intervened and suspended clinical trials in India until a proper monitoring mechanism was established.

In April 2013, amendments were made to regulate and improve the approval process for clinical trials, clinical trial inspection plans, registration of Ethics Committees, handling of serious adverse events (SAEs), compensation for injuries or deaths, informed consent processes, and other key areas. These changes led to a limited number of ethical clinical trials in India.

Cell and Gene Therapy (CGT) in India

The development of biotechnology tools paved the way for the emergence of Cell and Gene Therapy (CGT) (. As the need to test and approve cell and gene therapies for human use grew, the unique technical risks and ethical challenges associated with CGT trials required attention. Different government institutions in India formed committees and agencies to oversee and regulate CGT research and trials. India has 72 ongoing clinical trials in various phases and 11 approved products in the market, with many more in the pipeline.

Approved products CGT Products in the Indian Market

- ReliNethra®
- Stempeucell®
- Trichosera®
- Cutisera®
- Perioptisera®
- Cartigrow™ Chondron
- Ossgrow™
- Apceden®
- DermACELL®
- UreGrow®
- NexCAR19™

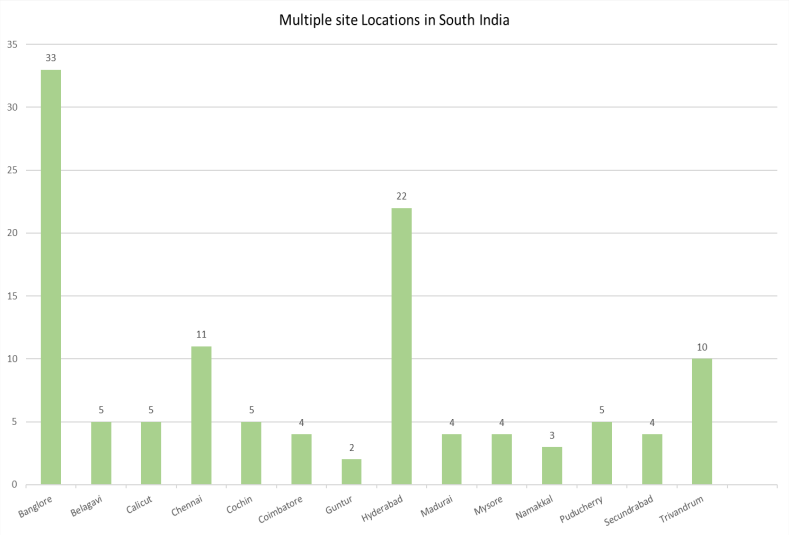

Figure 2: Graphical representation of cities having multiple trial site locations in South India

Ongoing Clinical Trials in India

India has gained global recognition for introducing accessible and affordable CAR-T Cell therapy in April 2024. The President of India, Ms. Droupadi Mormu, launched the country's first homegrown anticancer CAR-T cell therapy, NexCAR19, developed by collaborating with IIT Bombay, Tata Memorial Hospital, and Immuno-ACT. This achievement is expected to attract more instances of academia-industry synergy in India. Additionally, a new Haemophilia A gene therapy is under development in India and is the first of its kind to be approved for human trials. The Union Minister of Science and Technology has expressed optimism about the potential for manufacturing the vector in India and proceeding with clinical trials. Furthermore, a therapy for sickle cell disease (SCD) is being tested at All India Institute of Medical Sciences(AIIMS), approved by the FDA, and is expected to be available in the market by 2025.

India's unique approach to advancing technology and bringing it to market has garnered attention. The global gene therapy market, valued at $9.0 billion in 2023, is projected to grow at a CAGR of 21.4% to reach $23.9 billion by 2028. This growth is driven by factors such as increasing regulatory approvals, expanding clinical research in genomics, rising popularity of advanced targeted therapies, and the integration of AI. The Indian gene therapy market was valued at $0.67 billion in 2023 and is expected to grow further. Several factors contribute to the market's growth, including private sector investments, increasing prevalence of genetic disorders, and advancements in gene editing technologies. However, challenges such as high costs of gene therapy products, regulatory hurdles, and limited healthcare infrastructure hinder market growth. Despite these difficulties, the rising trends of personalized medicine, increasing collaborations between domestic and international biotech firms, and technological innovations in delivery mechanisms are poised to facilitate robust market growth.

CGT Regulation in India

The Guidelines for Stem Cell Research and Therapy in 2007 marked a significant step towards regulating CGT research and trials. In 2010 the Central Drugs Standard Control Organization (CDSCO) established the Cell Biology-Based Therapeutic Drug Evaluation Committee (CBBTDEC) to review cell therapy-based clinical trials. Following public consultation, the Guideline for Stem Cell Research 2007 was revised and released as the National Guidelines for Stem Cell Research (NGSCR-2013). Subsequent scientific and technical advancements led to updates in the NG-

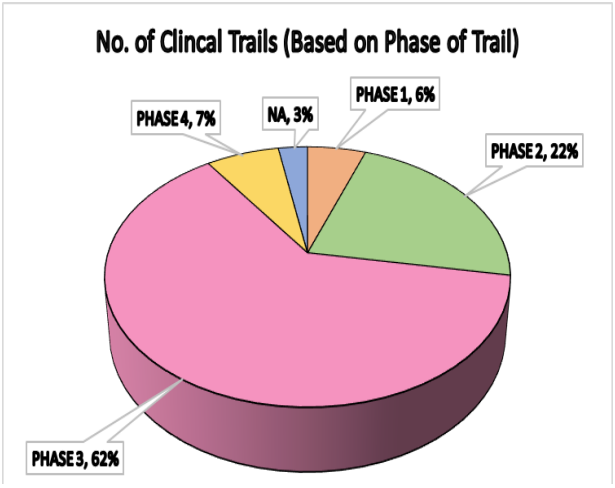

Figure 3: A pie chart representing the number of clinical trials based on the phase of the trial in percentage

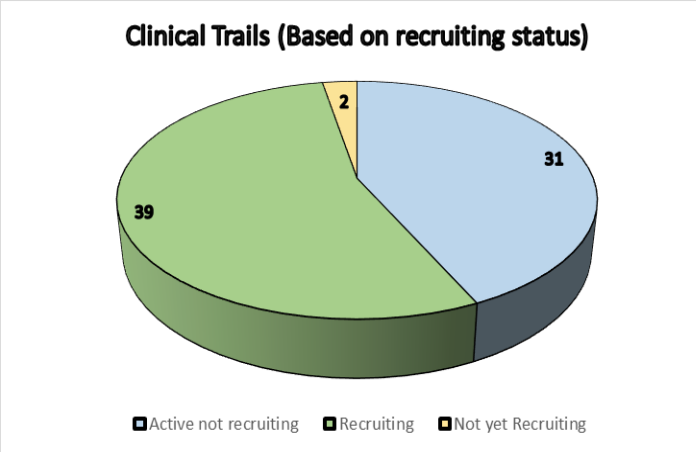

Figure 4: A pie chart representing the number of clinical trials based on recruiting status in percentage

SCR 2017, including a list of approved indications for hematopoietic stem cell transplantation (HSCT) and strengthened mechanisms for reviewing and monitoring clinical research.

The National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017, developed by the Indian Council of Medical Research (ICMR), provide ethical guidelines for all biomedical, social, and behavioral science research involving human participants, their biological material, and data. In 2019, the CBBTDEC was replaced by the Subject Expert Committee (SEC), an advisory committee to the DCGI responsible for evaluating scientific and technical matters related to new drugs, clinical trials, and new medical devices.

In 2019, the CDSCO recognized gene therapy products (GTPs) as a 'new drug' and introduced rules and guidelines for their development and testing. The National Guidelines for Gene Therapy Product Development and Clinical Trials were framed based on the FDA and EMA guidelines. The Gene Therapy Advisory and Evaluation Committee (GTAEC) was constituted by the Department of Health Research (DHR), the Ministry of Health and Family Welfare, and the Government of India.

In addition to the NGSCR-2017

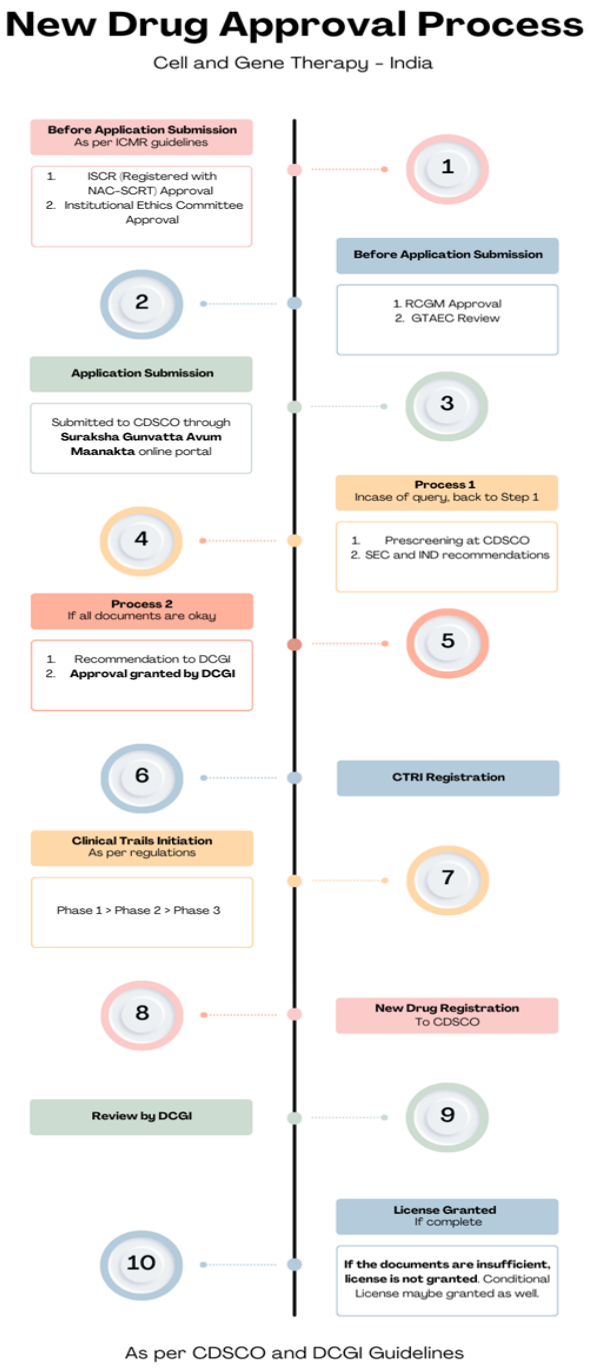

Figure 5: New Drug Approval Process

and the National Guidelines for Gene Therapy Product Development and Clinical Trials, the National Guidelines for Hematological Cell Transplantation-2021 (NGHCT) and Evidence-Based Status of Stem Cell Therapy for Human Diseases – 2021 were released by the ICMR to clarify the distinction between proven/established therapy and unproven/experimental therapy, which

often led to misuse for commercial benefits.

In 2022, the amended New Drugs and Clinical Trials (Amendment) Rules, 2022, under the Drugs and Cosmetics Act 1940, replaced the term "stem cell-derived product" with "cell or stem cell-derived product." This change requires CGTPs to comply with the Ministry of Environment, Forest, and Climate Change regulations, as they cover genetically engineered organisms and cells.

Other regulatory bodies, such as the Review Committee on Genetic Manipulation (RCGM), which operates under the DBT, monitor the safety of ongoing research projects involving hazardous microorganisms, genetically engineered organisms, and their products. All relevant acts, rules, and guidelines are accessible through the websites of the concerned government agencies.

The Clinical Trial Registry of India (CTRI) is a government body that ensures transparency in clinical trials by requiring registration of all clinical trials conducted in India involving human participants and interventions. The Institutional Bio-Safety Committee (IBSC) is a statutory committee within organizations that reviews research involving genome modification, ensuring adherence to bio-safety guidelines for CGTP development and preclinical testing. The Data Safety Monitoring Board (DSMD) is an independent body of experts that monitors patient safety and efficacy in clinical trials by reviewing data collected from all trial sites.

Specific considerations regarding Chemistry, Manufacturing, and Control (CMC), GMP Requirements, and preclinical and clinical testing models for CGTPs are outlined in the NGSCR – 2017 and National Guidelines on Gene Therapy Product Development and Clinical Trials 2019.

Abbreviations

- CGT – Cell and Gene Therapy
- IT – Information Technology
- SAE – Serious Adverse Events
- HSCT – Human Stem Cell Therapy
- ICMR – Indian Council of Medical Research
- CBBTDEC – Cellular Biology Based Therapeutic Drug Evaluation Committee
- CDSCO – Central Drugs Standard Control Organisation
- DCGI – Drugs Controller General of India
- GTPs – Gene Therapy Products
- CGTPs – Cellular and Gene Therapy Products
- ATMPs – Advanced Therapy Medicinal Products
- FDA – Food and Drug Administration
- EMA – European Medicines Agency
- USA – United States of America
- DBT – Department of Biotechnology
- DHR – Department of Health Research
- GE – Genetically Engineered
- ISCR – Indian Society for Clinical Research
- IND – Investigational New Drug
- CAR – Chimeric Antigen Receptor
- IIT – Indian Institute of Technology
- SCD – Sickle Cell Disease
- AIIMS – All India Institute of Medical Sciences
- CAGR – Compound and Annual Growth Rate
- AI – Artificial Intelligence

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REGULATION UPDATE AND ANALYTICAL FOR CELL AND GENE

Shing-Mou Lee

CEO

EMO Biomedical Corporation

Current Regulation on Cell and Gene Therapeutics in Taiwan

The Ministry of Health and Welfare (MOHW) of Taiwan announced two important Acts, Regenerative Medicine Act and Regenerative Medicine Products Act, related to the Cell and Gene Therapeutics (CGTs) in June, 2024.

Before the two Acts announcement, MOHW already announced "Guidance for Registration and Reviewing of Human Cell Therapy Products" and "Guidance for Registration Reviewing of Human Gene Therapy Products" for regulating cell and gene therapy products In 2022. The rapid sterility test special for cell therapy product is also listed in Taiwan Pharmacopeia v.9 published in 2022.

Under these Acts and guidelines, The CGTs are regulated as drug products and the manufacturing of CGTs should be compliant with PICs/GMP requirements in Taiwan. The regulatory environment in Taiwan has being much more complete and clear for developer of advanced CGTs.

Regulations announced recently, have great impact on the development of CGTs in academic and promotion of industrial sectors. Cell and gene therapies have been playing an increasing important position in innovative drug development. Rapidly increasing number of new innovative CGT companies and clinical trials has been observing in past few years in Taiwan.

Quality by Design concept is introduced in CGT production

As conventional drugs production, the concept of quality by design (QbD) is introduced in the current guidance to emphasize on the risk assessment and quality assurance of manufacturing of CGTs.

Quality control is a fundamental aspect for assuring the safety and efficacy of drug products. Testing of drug products is performed at intermediate and final manufacturing stages to confirm that they meet established specifications as defined in a marketing authorization.

Product quality attributes need to be tested for obtaining the necessary information about product quality, safety, and efficacy during early development. Information gathered from those test results assists to define the critical process parameters (CPPs) of manufacturing process and

L METHOD DEVELOPMENT CHALLENGES THERAPEUTICS (CGT)

mechanism of action (MOA) related critical quality attributes (CQAs). CQAs and CPPs of manufacturing process need to be defined and controlled by suitable analytical methods.

CQAs are physical, chemical, biological, microbiological properties that ensure product desired quality, including safety, purity, identity, potency. CPPs are variable elements of the manufacturing process that influence CQAs. The development and validation of analytical methods to define the CQAs and CPPs for CGTs are very challenging, because of the inherent heterogeneity of raw materials and complexity of mechanism of action (MOA).

The Regulation on CGTs update in Taiwan and Worldwide

Manufacturing Changes and Comparability

Manufacturing process changing is almost unavoidable during the development of CGT product. Any manufacturing change is required submit results of comparability study. Comparability is an essential requirement for quality assurance when changing the manufacturing process of CGTs.

In July 2023, US FDA announced "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products (CGTs) Draft Guidance for industry". Japan MHLW also announced "Guideline for Comparability of Human Cell-Processed Products Subject to Change Their Manufacturing Process." in March 2024.

Potency Test and Potency Assurance Strategy

A potency test must reflect the product's MOA but also correlate to the safety and efficacy data generated in preclinical models and clinical studies. A qualified potency assay would ideally be used to analyze all preclinical lots that are manufactured and verified prior to commercialization. Potency test should be quantitative bio assay and be able to apply in lot release, stability, and comparability study.

In December 2023, US FDA announced "Potency Assurance Strategy for Cellular and Gene Therapy Products-Draft Guidance for Industry". This draft guidance provides recommendations for developing a science- and risk-based strategy to help assure the potency of a human CGT product. The goal of a potency assurance strategy is to ensure that every lot of a product released will have the specific ability or capacity to achieve the intended therapeutic effect.

FDA fully expects Potency Assurance Strategy to grow over time, requiring refinement during development, resulting in an increasingly precise product potency description, ideally involving quantitative bioassays and manufacturing and clinical data.

Chimeric Antigen Receptor, CAR-T Cell Product

Up to May 2023, six CAR-T cell therapy products, Kymriah, Yescarta, Tecartus, Breyanzi, Abecma, and Carvykti, have been approved in US and EU. Kymriah is also approved in Taiwan.

The efficacy of autologous CAR-T products is acceptable by most of the regulatory authority. However, the safety and product quality consistency, particularly for allogenic off-the-shelf products, are still concerned by regulator.

In January 2024, US FDA announced "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products Guidance for Industry". The guidance highlights the importance of risk assessment—considering the safety and quality of the product.

Within such risk assessment, future actions such as comparability studies or analytical-method revalidation can be found as necessary steps prior to implementing changes. The FDA guidance states that an initial IND submission should include: "A description of the assay, including the flow cytometry antibody panel and the gating strategy used to define each cell population detected" and that "live/dead strain should be included in the flow cytometry panel."
In February 2024, a similar "Guidance for the Development strategy of Chimeric Antigen Receptor, CAR-T Cell product" was announced by Taiwan MOHW.

The Strong Support of CGTs industry Development in Taiwan-EMO Biomedicine

EMO Biomedicine, a Taiwan-based company, was founded in 2004. EMO is dedicated to developing therapeutic cell-based products and human cell-related analytical methods. EMO has been offering professional and comprehensive high quality testing, contract research and cell processing services since 2007. EMO has been a qualified CRO for pharmaceuticals by Ministry of Economic Affairs, Taiwan since 2013.
EMO's Testing Lab is in compliance with ISO/IEC 17025 and accredited by Taiwan Accreditation Foundation (TAF) and Taiwan FDA (TFDA). The TAF accredited testing scope covers cell-based products, biologics, cell culture supernatant, and whole blood. Accredited testing item includes MSC surface markers, NK cytotoxicity, Quantitative IDO, and safety test (mycoplasma, endotoxin, direct inoculation sterility test, rapid sterility test). The safety tests for CGTs are also compliant with pharmacopeia of Taiwan, US, or EU.
Most of identity, functionality, and potency assays are customized depend on client's request. IDO quantitative assay is an EMO's proprietary patent flow cytometry-based method for measuring immunosuppressive capability of MSC product in vitro and predict efficacy in vivo.
EMO's Testing Lab and manufacturing facility have passed over 34 audits or inspections by TFDA, TAF and CDC for its technical competence, management system, and GTP compliance since it established.
EMO's manufacturing facility and quality management systems for therapeutic cell-based product has been inspected by TFDA for the compliance with Good Tissue Practice (GTP) guidance. In 2019, EMO's Cell Processing Unit (CPU) received certificate for processing, culture, and storage of cell therapy product with every three years extension inspection by TFDA.
EMO also offers support for clinical trial and contract manufacturing services for cell therapy products in compliance with Good Tissue Practice (GTP) under the regulation of Taiwan. Our experts have extensive experience in handling immune and mesenchymal stromal cells. EMO is ready to offer a one-stop complete service, including manufacturing and comprehensive testing, for local and oversea clients.

EMO's Testing Services for Cell-Based Therapeutics		
Safety / Microbiology Testing Services	Identity Test / Customized Test	
Mycoplasma Testing and Verification Taiwan Pharmacopoeia 5063 & EP2.6.7&2.6.21	MSC	MSCs Surface Marker Analysis
		Suppression of T cell proliferation
Endotoxin Testing- Kinetic Chromogenic LAL Assay Taiwan Pharmacopoeia 3085;& USP<85>		IDO Quantification Assay
	CAR-T	CAR-T Surface Marker Analysis
		Cytotoxicity assay
Direct Inoculation Sterility Test & Verification Taiwan Pharmacopoeia 3071;& USP<71>	Immune Cell product	Lymphocyte, DC, γδT Surface Marker Analysis
		Mixed Lymphocyte Reaction(MLR)
Rapid Sterility Test and Verification Taiwan Pharmacopoeia 5097;& EP2.6.27		NK Cell Cytotoxicity assay
		Customized Cytotoxicity assay
		Cytokine analysis(Intracellular/Secretion)
		Protein expression analysis

EMO's Contract Research Services for Pharmaceuticals
Tailored cell-based bioassay /potency assay for biologics, including biosimilars, peptides, monoclonal antibodies, growth factors and cytokines
ADCC (Antibody-dependent Cell-mediated Cytotoxicity)
CDC (Complement-dependent Cytotoxicity)
ADCP (Antibody-dependent Cell-mediated Apoptosis)
Cell Binding Assay
Cell Differentiation
Cell Subset Analysis
Cell Proliferation & Cytotoxicity (spectrophotometric- and flow cytometric-based)
Cytokine Response Assay
Ligand Binding Assay
IL-2 Stimulation Assay (pSTAT5)
MLR (Mixed Lymphocyte Reaction)
Neutralization Assay
Receptor Occupancy (RO)

EMO's Mileston

No.	Date	
1	2007/06/20	EMO obtained the Certificate of Accreditation as a "Testing Laborator
2	2009/11/20	EMO obtained the Certificate of Accreditation as a qualified "Drugs T
3	2010/12/09	EMO accepted a cell therapy contract clinical study and inspected by T
4	2016/09/01~ 09/02	EMO passed the GTP compliant inspection by TFDA for its proprietar
5	2016/12/09	EMO Received "Excellence Award of Laboratory Biorisk Managemer TAIWAN.
6	2017/07 ~ 2019/8	EMO completed patient enrollment of MSCs product - RegStem ® Pha
7	2019/07/01	EMO developed proprietary IDO quantitative assay, for measuring imr testing service to local and oversea clients.
8	2019/12/26	EMO approved by the MOHW as a GTP-compliant Cell Processing U and Medical Device''(hereinafter referred to as the Specific Regulation product (RegStem ®) to treat degenerative arthritis and knee cartilage
9	2021/05/11	EMO's IDO quantitative assay related invention, "Use of Mesenchyma
10	2022/04/14	The first hospital-Far Eastern Memorial Hospital was approved to use in Taiwan.
11	2022/01/24	EMO's RegStem ® MSC phase 1 trial results was published in ISCT (85. Title: Infrapatellar fat pad-derived mesenchymal stromal cell produ
12	2022/07/01	EMO successfully renewed its TAF accreditation in July to maintain th Test" which is in accordance with Taiwan Pharmacopoeia (5097) and s
13	2022/12/26	EMO's CPU received an extension of its GTP certification, extending hospital- Hualien Tzu Chi Hospital was approved to use RegStem ® fo
14	2023/04/17	The third hospital- Cardinal Tien Hospital was approved to use RegSte Taiwan.
15	2024/11/06	EMO's IDO quantitative assay related invention, "Use of Mesenchyma

e & Achievements

Details
y; No. 1809" from Taiwan Accreditation Foundation (TAF), in compliance with ISO/IEC 17025:2005.
esting Laboratory; No. D005" fromTaiwan FDA.
TFDA for the GTP compliance.
y RegStem ® MSC product phase Iclinical trial.
t System Implementation" from Centers for Disease Control (CDC), Ministry of Health and Welfare,
ase 1 clinical trial for treatment of osteoarthritis.
munosuppressive capability of MSC product, was certificated by TAF and started to provide the IDO
nit (CPU) for processing, culture, and storage cell therapy product under Specific Medical Examination n). EMO is the first CPU in Taiwan to receive approval for providing autologous adipose-derived MSC e defects .
al Stem Cells in Treating Immune-related Disease", was issued by Taiwan Patent Office.
RegStem ® for treating degenerative arthritis and knee cartilage defects under the Specific Regulation
The International Society for Cell and Gene Therapy) official Journal - Cytotherapy 2022 Jan; 24(1):72- ct for treatment of knee osteoarthritis: a first-in-human study with evaluation of the potency marker
he accreditation status. At the same time announced a new TAF certified testing item "Rapid Sterility specially used for the therapeutic cell product.
the validity to December 25, 2025. In addition to the Far Eastern Memorial Hospital, the second or treating degenerative arthritis and knee cartilage defects under the Specific Regulation in Taiwan.
em ® for treating degenerative arthritis and knee cartilage defects under the Specific Regulation in
al Stem Cells in Treating Immune-related Disease" has been issued by US Patent Office (USPTO).

ACTO MEE

LATE BREAKING ABSTRACT WILL B

TING 2024

E PUBLISHED AT THE ACTO TIMES

FIND THE PROGRAM BOOK HERE:

SIGLEC6 CAR-T CELLS OVEREXPRESSING THE IL12P40 SUBUNIT ENHANCE THEIR ANTI-ACUTE MYELOID LEUKEMIA ACTIVITY BY SECRETING HIGHER LEVELS OF IL23

Bing Wang, Ruiting Guo, Shujing Guo, Jile Liu, Mingfeng Zhao

Department of Hematology, Tianjin First Central Hospital

CAR-T therapy provides a new option for AML patients. Research has shown that Siglec6 is a good target for CAR-T treatment of AML. However, due to its poor performance in persistent tumor killing, Siglec6 CAR-T has not yet been used in clinical practice. Therefore, further optimization of CAR-T targeting Siglec6 is urgently needed. By analyzing clinical CAR-T treatment data, We found that the level of IL12p40 in patient serum is directly proportional to CAR-T amplification time and efficacy. Therefore, this study designed a fourth generation Siglec6 CAR-T expressing IL12p40. The results showed that although IL12p40 is a shared subunit of IL12 and IL23, the fourth generation CAR-T can secrete higher levels of IL23 rather than IL12, and its killing ability and persistence are better than the original CAR-T Based on the experimental results, we believe that Siglec6-IL12p40 CAR-T enhances its killing function and delays exhaustion by secreting higher levels of IL23. This study will further explore its molecular mechanism. The aim of this study is to improve the efficacy of Siglec6 CAR-T and provide new strategies for the treatment of AML, which has great clinical translational potential.

NEPHROTOXICITY OF CAR-T THERAPY IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Zihan Chen, Yegan Chen, Jiaying Liu, Yingjun Sun, Lingyu Zeng, Junnian Zheng, Kailin Xu, Li Li, Hai Cheng, Jiang Cao

Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221002, China

Chimeric antigen receptor T (CAR-T) cell therapy has achieved impressive efficacy in treating relapsed and refractory multiple myeloma (R/R MM). Nephrotoxicity after CAR-T cell therapy has rarely been reported. We investigated the occurrence and clinical outcomes of acute kidney injury (AKI) in 111 patients with R/R MM after CAR-T cell therapy. Thirteen patients (12.1%) developed AKI within one month of CAR-T therapy, of which 11 had grade 1 AKI, 1 had grade 2, and 1 had grade 3. Eleven (84.6%) cases resolved within 1 month after CAR-T cell therapy. The baseline tumor burden was an independent risk factor for the development of AKI. The finding of a high baseline tumor burden or hyponatremia after CAR-T cell therapy and close monitoring of lactate dehydrogenase, uric acid, interleukin (IL)-5 and IL-10 levels were helpful in predicting the development of AKI. The incidence of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were similar between the AKI and non-AKI groups. There was also no significant difference in clinical efficacy between the two groups. These findings suggest that AKI is reversible and does not affect the clinical outcome in R/R MM patients receiving CAR-T cell therapy.

COMPLEX ASSOCIATION OF BODY MASS INDEX AND OUTCOMES IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA TREATED WITH CAR-T CELL IMMUNOTHERAPY

Yingjun Sun, Xiaoxue Zhang, Zihan Chen, Lingyan Shao, Jiaying Liu, Dandan Wang, Yegan Chen, Hai Cheng, Kailin Xu, Jiang Cao

Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, 221002, China

Chimeric antigen receptor-T (CAR-T) cells have exhibited remarkable efficacy in trea ing refractory or relapsed multiple myeloma (R/R MM). Although obesity has a favorable value in enhan ing the response to immunotherapy, less is known about its predictive value regarding the efficacy and prognosis of CAR-T cell immunotherapy. We conducted a retrospective study of 111 patients with R/R MM who underwent CAR-T cell treatment. Using the body mass index (BMI) classification, the patients were divided into a normal-weight group (73/111) and an overweight group (38/111). We investigated the effect of BMI on CAR-T cell therapy outcomes in patients with R/R MM. The objective remission rates (ORRs) after CAR-T cell infusion were 94.7% and 89.0% in the overweight and normal-weight groups, respectively. The duration of response (DOR) and overall survival (OS) were not significant difference between BMI groups. Compared to normal-weight patients, overweight patients had an improved median progression-free survival (PFS). There was no significant difference in cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) between the subgroups. In terms of hematological toxicity, the erythrocyte, hemoglobin, platelet, leukocyte and neutrophil recovery was accelerated in the overweight group. Fewer patients in the overweight group displayed moderate per cent CD4 and CD4/CD8 ratios compared to the normal-weight group. Furthermore, the per cent CD4 ratios were positively correlated with the levels of cytokines [interleukin-2 (IL-2) (day 14), interferon gamma (IFN-γ) (day 7), and tumor necrosis factor alpha (TNF-α) (days 14 and 21)] after cells infusion. On the other hand, BMI was positively associated with the levels of IFN-γ (day 7) and TNF-α (days 14 and 21) after CAR-T cells infusion. Overall, this study highlights the potential beneficial effect of a higher BMI on CAR-T cell

NEPHROTOXICITY OF CAR-T THERAPY IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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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.

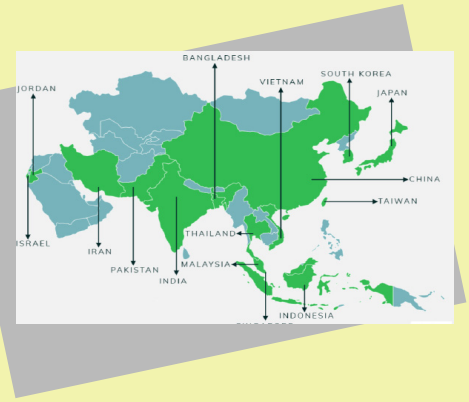
Since its establishment stemming from the ISCT Asian Regional Meeting, ACTO has evolved into a dynamic organization with a broad presence covering 15 regional territories, including Bangladesh, China, India, Indonesia, Iran, Japan, Jordan, Israel, Korea, Malaysia, Taiwan, Thailand, Singapore, Vietnam, 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

1

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.

2

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.

3

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.

4

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.

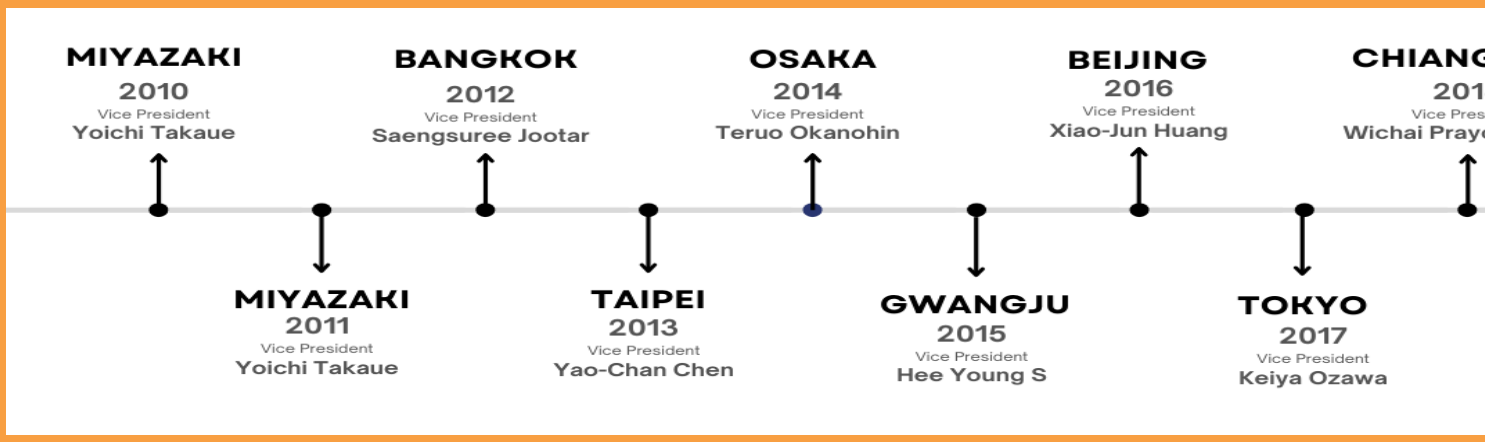
5

REGULATORY FRONTIERS

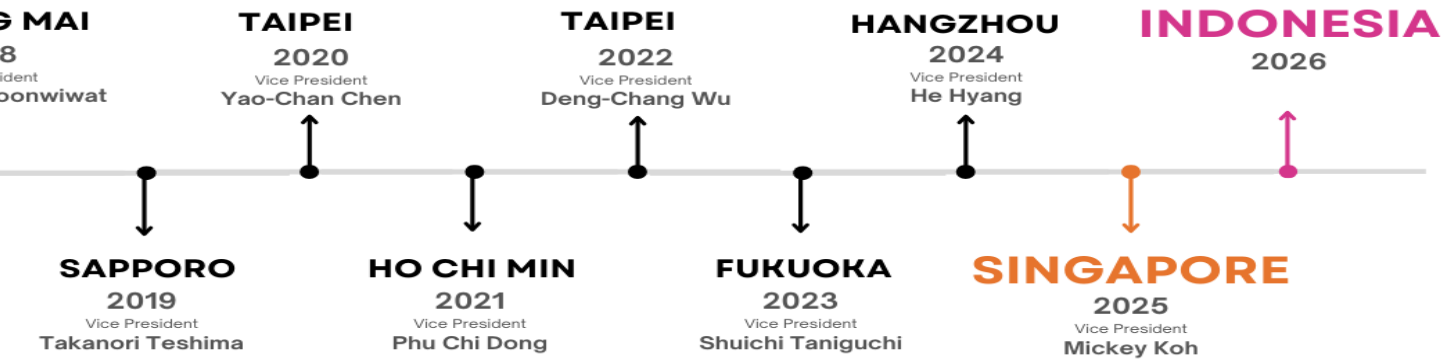
The diverse regulatory frameworks and rich cultural tapestry across Asian regions stand as influential forces shaping the intricate process of CGT in the region. In navigating this dynamic landscape, each nation brings its own set of regulations, reflecting unique perspectives on ethical considerations,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

OUR JOURNEY

Over the years, the ACTO meetings became a cornerstone for professionals in the field, providing a platform for networking, sharing knowledge, and forging international partnerships. As the organization evolved, reflecting the dynamic landscape of CGT in the Asia-Pacific region. The ACTO meeting was started from the first International Society of Cellular Therapy (ISCT) Asian-Pacific Regional Meeting 2010 in Japan. The primary objective of this gathering is to facilitate the exchange of knowledge and expertise among researchers, clinicians, business professionals, and regulators in the realm of CGT.

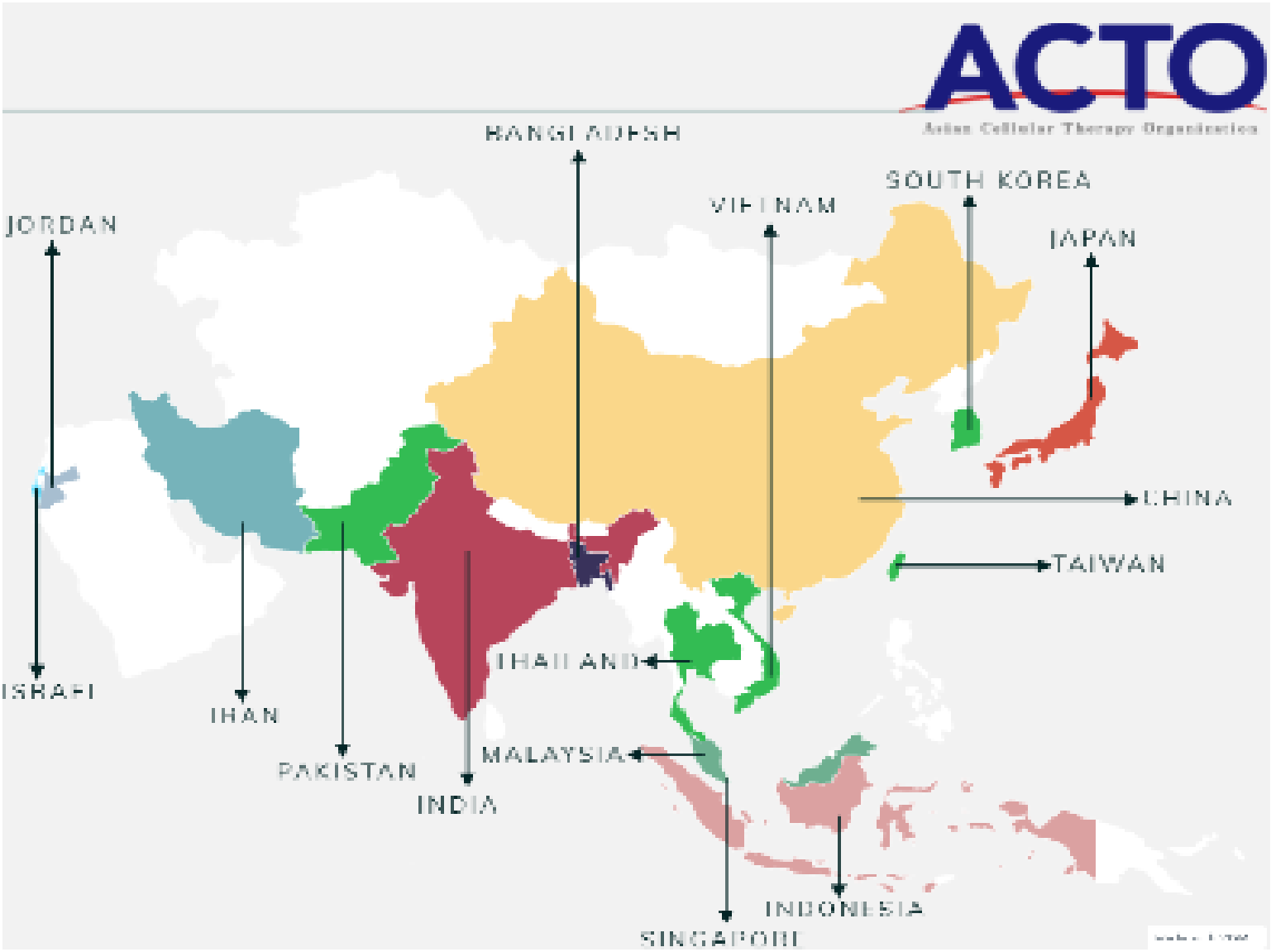


THROUGH TIME



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.

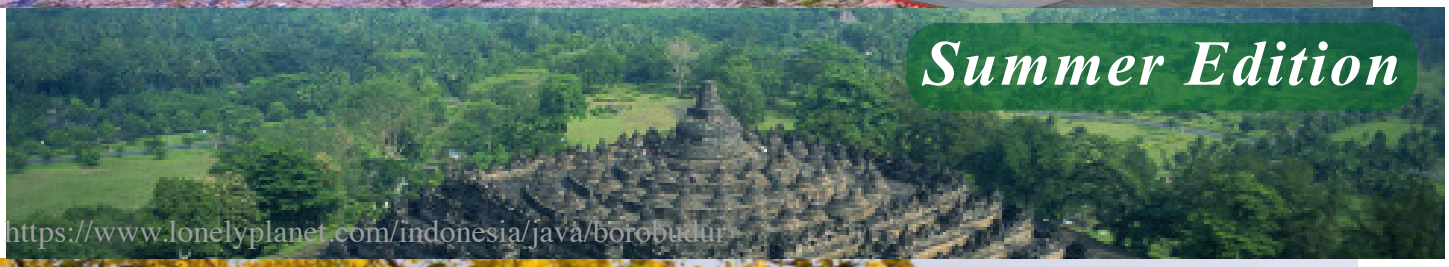
REGIONAL TERRITORIES

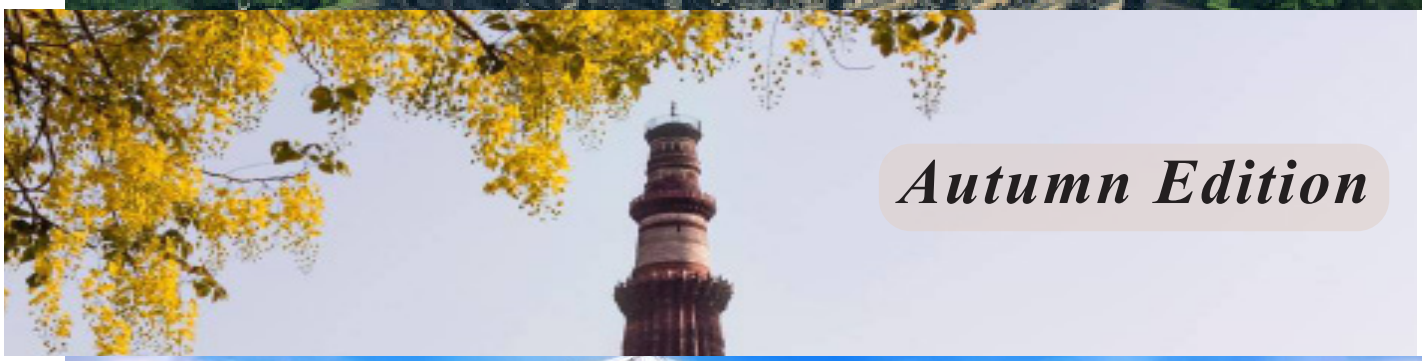


As of the present moment, the Asian Cellular Therapy Organization (ACTO) has seen the enthusiastic engagement of 15 regional territories in its annual meetings. This collective involvement underscores the organization's commitment to fostering collaboration and knowledge exchange among diverse regions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

THE ACTO TIMES PRESENTING

ACTO NEW SEASONAL E-MAGAZINE





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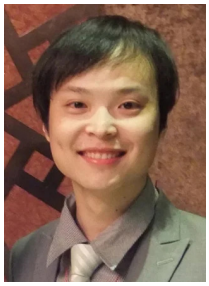

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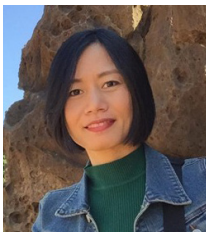

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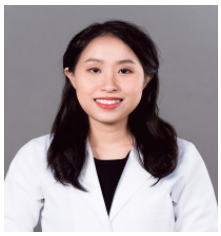

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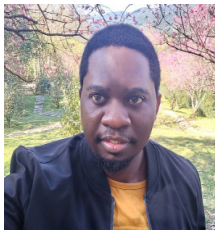

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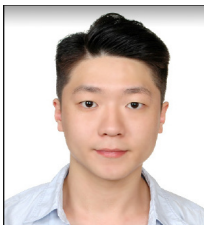

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RECRUITMENT

"The ACTO Times" is excited to extend an invitation for passionate individuals to join our esteemed editorial team. We are currently seeking dynamic and dedicated professionals to serve as Associate Editors, contributing their expertise to shape the publication's content. This call encompasses both Regional Associate Editors, who will bring a nuanced understanding of CGT developments in specific Asian regions, and Academic Associate Editors, who will lend their scholarly insights to enrich the depth and breadth of our articles. In addition, "The ACTO Times" is calling for an Assistant Editor to play a pivotal role in supporting the editorial process. We are also opening opportunities for Regional Reporters, providing a platform for enthusiasts to contribute region-specific insights and updates. If you are driven by a passion for advancing CGT and wish to be part of a dynamic editorial team, we invite you to apply and become an integral part of shaping the narrative of CGT in Asia.

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- Europe
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Rita_Editor-in-Chief The ACTO Times
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Asian Cellular Therapy Organization