The ACTO Times

Asian Cellular Therapy Organization

Spring Edition

The 14th ACTO Annual Meeting Report

Preface

ACTO Chairperson

Dear ACTO members,

It is a great pleasure for us to start publication of The ACTO Times today. ACTO was organized in 2010 by the group of scientists in the field in Asia. Majority of the starting member were also the member of ISCT.

The first meeting in Miyazaki was organized by Dr. Yoichi Takaue, National Cancer Center, Tokyo, Japan under collaboration among Dr. Yao-Chan Chen, National Taiwan University, Mickey Koh, HSA, Singapore, H.Y. Shin, Seoul National University, Korea, Saengsuree Jootar, Mahidol University, Thailand, Abbas Ghaderi, Shiraz University, Iran, Xue-Tau Cao, Second Military Medical University, China, Xiao-Jun Huang, Peking University, China, Hu Chen, 307 Hospital, Beijing, China and Kaiyan Liu, Peking University, China.

We all agreed to form a society that matches the Asian situation because ISCT meetings became too expensive for Asian country members. Since then, we have been able to organize annual meetings in several cities in Asia. A unique feature of ACTO is collaboration among three key players in the field: academia, industry, and regulatory agencies. Without the joint efforts of these three players, we cannot achieve success in treating patients who need new therapies. Finally, we have been able to organize The ACTO Times committee to publish information related to ACTO activities. Prof. Rita Yen-Hua Huang, Taipei Medical University kindly accepted the responsibility as the Editor-in-Chief and named the publication ‘The ACTO Times’. The activity of The ACTO Times was approved at the executive committee meeting held on November 7, 2023, at the 14th ACTO meeting in Fukuoka. The ACTO Times will be published four times a year. For The ACTO Times committee members, we will have associate editors from each country as well as the Chairpersons of the regulatory committee and industry committee.

Your inputs are highly appreciated and we will improve the quality of publications.

Best regards,

Akihiro Shimosaka

Editorial Greeting

The ACTO Times Editor-in-Chief

Dear Readers and Contributors,

I am thrilled to welcome you as the Editor-in-Chief of The ACTO Times, the esteemed publication of the Asian Cellular Therapy Organization (ACTO). Together, we embark on a journey dedicated to advancing the field of cellular therapy in Asia.

As the Editor-in-Chief, I am honored to lead a team of passionate individuals committed to deliver a magazine that captures the latest trends, breakthroughs, and challenges of cell and gene therapy (CGT). Our intention is to provide a comprehensive and up-to-date resource that resonates with professionals, researchers, and enthusiasts alike.

The ACTO Times is more than just a publication; it is a platform where knowledge is exchanged, connections are formed, and ideas are shared. We believe in the power of dialogue and collaboration to drive innovative solutions and push the boundaries of cellular therapy in our region.

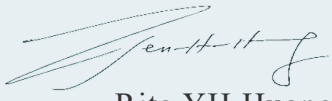
Through the diverse articles in CGT preclinical research, clinical trials, product development, and global regulation, we aim to present a holistic view of cellular therapy in Asia. We warmly welcome contributions from experts and thought leaders, both from within and beyond Asia, as their collective insights will shape the narrative and inspire our readers.

Together, we will uncover the tremendous potential of cellular therapy and its impact on transforming lives. By fostering a rich sense of community and future collaboration, we will build a reservoir of knowledge that propels the field forward and brings hope to those in need.

I invite you to actively engage with The ACTO Times, contribute your expertise, share your discoveries, and participate in the vibrant discourse that we aim to foster. Your involvement is vital in shaping the future of cellular therapy, and I eagerly anticipate your contributions. Stay tuned for upcoming editions as we provide valuable insights, thought-provoking articles, and the latest updates on cellular therapy. I look forward to collaborating with you to make The ACTO Times a dynamic and influential platform for advancing cellular therapy in Asia and beyond.

Thank you for being part of this exciting venture.

Warmest regards,



Rita YH Huang

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"If we knew what we were doing,
it would not be called research, would it?"
- Albert Einstein-

CONTENTS

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.

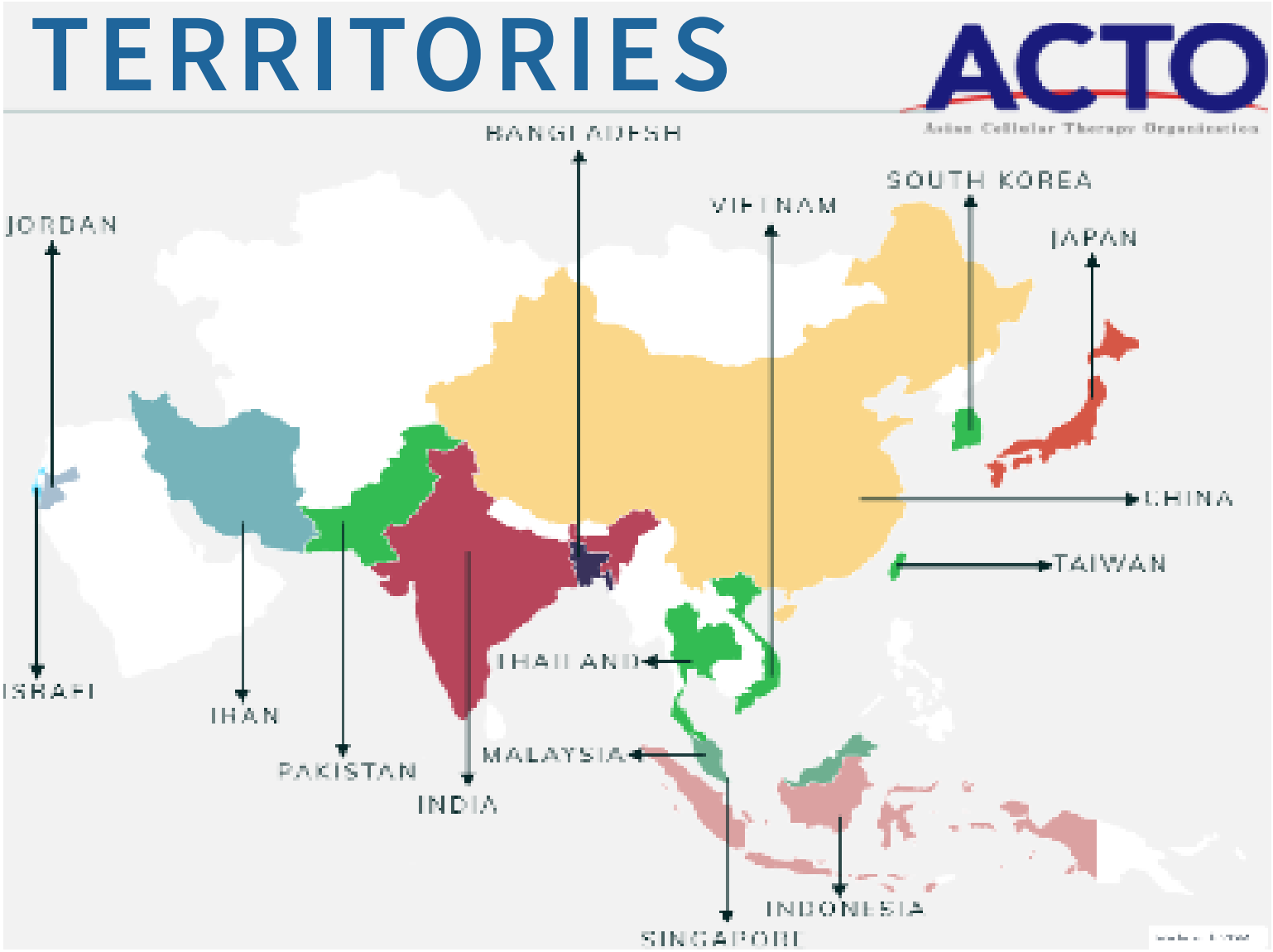
ACTO is dedicated to driving advancements in cell and gene therapy (CGT), including research, clinical applications, industry collaborations, and global regulation. It seeks to facilitate collaborative environment where professionals, researchers, industry leaders, and regulatory agencies can come together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

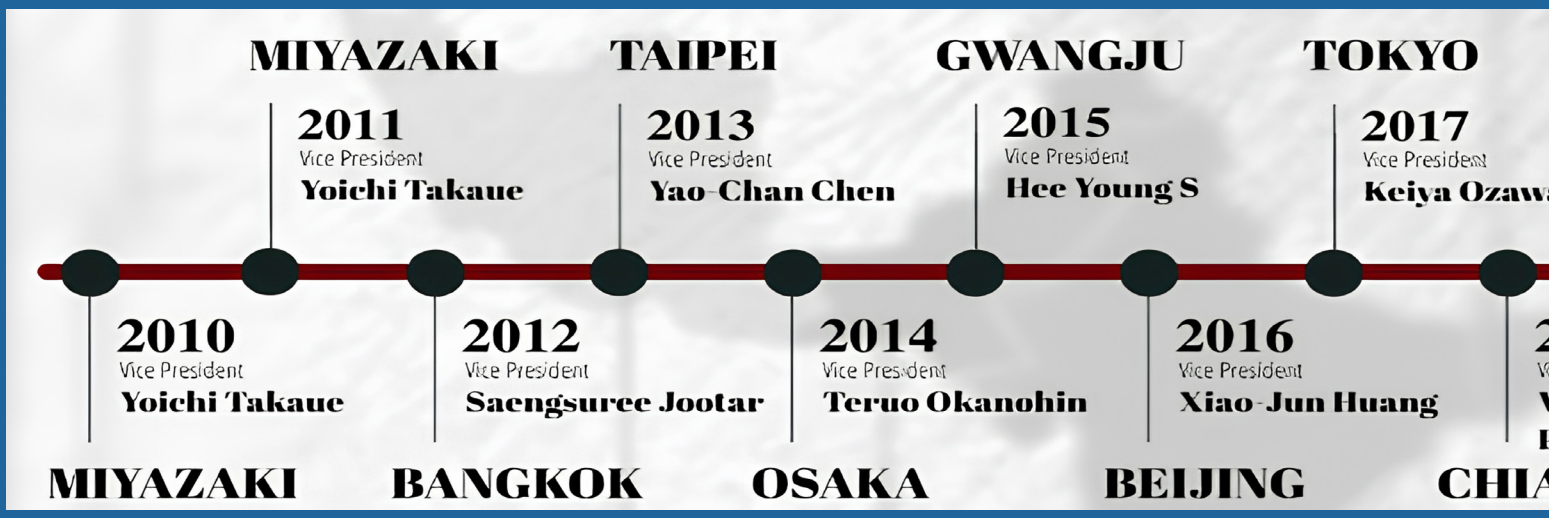
REGIONAL TERRITORIES



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.

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 countries, 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.

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 countries 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.

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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INTERVIEW WITH AKIHIRO SHIMOSAKA

ACTO CHAIRPERSON

Asian Cellular Therapy Organization (ACTO) plays a pivotal role in advancing the field of Cell and Gene Therapy (CGT) across Asia, focusing on regional impact and collaboration with institutions in the region. With its culturally sensitive approach, ACTO recognizes the diversity of practices and traditions within Asian countries, fostering collaboration with local institutions to ensure the development of tailored solutions that resonate with the unique needs and cultural contexts of Asian patients. By working closely with Asian institutions, ACTO promotes knowledge sharing, capacity building, and the adoption of best practices in CGT, contributing to the advancement of healthcare standards throughout the region.

The Asian Cellular Therapy Organization (ACTO) is a non-profit organization dedicated to promoting precision therapy for Cell and Gene Therapy (CGT) across Asia. Our mission is achieved through the organization of annual meetings that foster communication and collaboration among Asian countries and local institutions. Unique feature of the ACTO is close collaboration among academy, industry and regulatory agency in each country. By working closely with Asian institutions, we address the unique needs and cultural contexts of Asian patients.

ACTO actively collaborates with regulatory authorities and stakeholders to promote harmonized regulations and standards in the field of CGT. Our annual meetings, which draw participants from 15 Asian territories and other territory such as Europe and USA, provide a platform for staying abreast of the latest CGT regulations and clinical practices. These gatherings foster innovation and investment in the field.

Since 2010, we have hosted the ACTO Annual Meeting in several cities, including Japan (2010, 2011, 2014, 2017, 2019, 2023), Thailand (2012, 2018), Taiwan (2013, 2020, 2022), Korea (2015), China (2016), and Vietnam (2021). Our upcoming Annual Meetings will take place in China (2024) and Singapore (2025). Our goal is to ensure that all patients in Asia have access to the latest advancements in CGT.

Adapting global clinical advances to the Asian context is a top priority for ACTO. We collaborate with international partners to identify cutting-edge technologies and tailor clinical treatment approaches to meet the unique needs and challenges of Asian populations. Through collaboration and knowledge exchange between Asian and global experts, we facilitate the localization of global advancements in CGT. Our aim is to make these innovations relevant, accessible, and effective in Asian settings. By promoting adaptation and collaboration, ACTO strives to bring the benefits of global clinical advances to patients in Asia.

ACTO also places great importance on public awareness and talent education in the field of CGT. We collaborate closely with renowned global experts, physicians, and academic

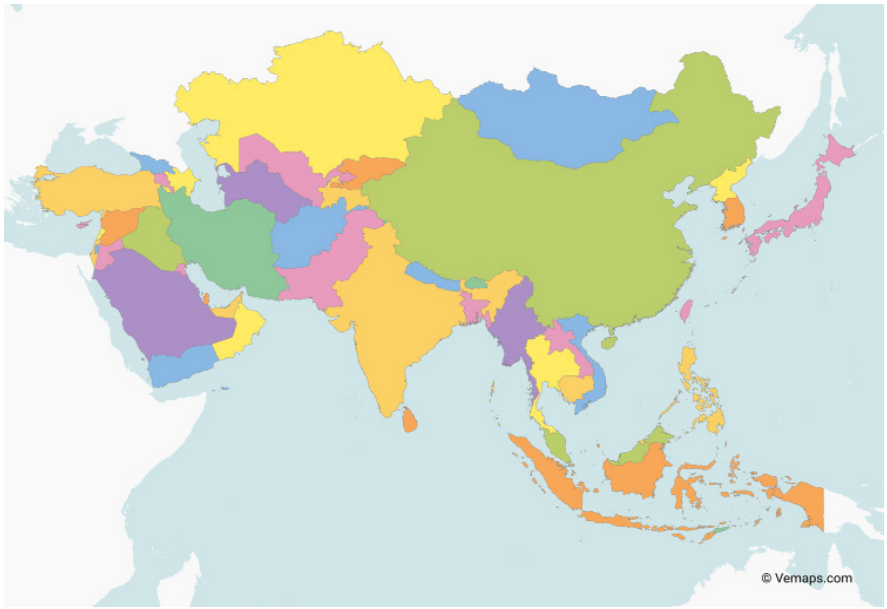
scientists to enhance public awareness of the potential benefits and challenges of current CGT practices. Our aim is to educate and engage patients, healthcare professionals, regulatory agencies, and the general public about the advancements and implications of CGT.

Technological innovation plays a pivotal role in driving the progress of CGT, with Asia leading in the development of cutting-edge technology and manufacturing platforms. ACTO actively collaborates with leading innovators and research institutions to foster technological advancements in the field. With your support, ACTO accelerates the translation of research discoveries into clinical applications and supports the development of next-generation CGTs that address unmet medical needs. By promoting collaboration and innovation, ACTO contributes to the advancement of CGT in Asia and beyond.

Asia's CGT landscape is rapidly advancing in research, clinical applications, regulatory frameworks, market demand, and international collaboration, poised to transform healthcare in the region. Here are some key projections for CGT in Asia:

1. Stem Cell Therapies: Asia is making significant strides in various stem cell therapies such as mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and hematopoietic stem cells (HSCs). These therapies hold potential hopes for treating conditions such as cardiovascular disease, neurodegenerative disorders, and orthopedic injuries.

> The Asian Cellular Therapy Organization (ACTO) is a non profit organization therapy for Cell and Gene Therapy (CGT) across Asia.



https://vemaps.com/asia-continent/as-c-05#google_vignette

2. Gene Editing Technologies: Asia is at the forefront of developing and applying gene editing technologies like CRISPR-Cas9 for targeted gene therapy. Researchers in the region are exploring gene editing approaches to address genetic disorders, cancer, and infectious diseases.

3. CAR-T Cell Therapy: Chimeric antigen receptor (CAR) T-cell therapy is gaining momentum in Asia as a potentially effective treatment for certain cancers, including leukemia and lymphoma. Clinical trials and efforts for commercialization are underway to make CAR-T cell therapy more accessible to patients in the region.

4. Gene Therapies: Asia is actively involved in the development of gene replacement therapies, which involve introducing functional copies of genes to correct genetic mutations. These therapies hold promise for some rare diseases, with ongoing research and clinical trials in the region.

For over a decade, ACTO has been dedicated to fostering collaboration with international partners to promote knowledge exchange, standard harmonization, and the global advancement of CGT. Moving forward, ACTO will continue its focus on patient-centered care, talent education, technological advancements, precise clinical applications, and the establishment of safe regulations. With your participation and enthusiasm, ACTO is primed to lead ongoing innovation and progress in CGT across Asia and beyond.

Summarized by Nova Yuli Prasetyo Budi, MD

POINTS TO CONSIDER FOR AUTOLOGOUS CELLULAR THERAPY

Akihiro Shimosaka, Ph. D.

Chairperson: *Asian Cellular Therapy Organization*

Director: *Research Foundation for Community Medicine*

The speech was delivered at Department of Pharmacology, College of Medicine, National Taiwan University on November 19th, 2023

Cellular therapy has become a crucial treatment modality for patients. However, regulation for autologous cellular therapy remains inadequate. CAR-T therapy is regulated as a 'drug' based on the marketing authorization system, even though processed CAR-T cells are intended solely for the patients who provided the cells for processing. Several issues persist within CAR-T cell therapy today.

1. Firstly, CAR-T cell technology was initially developed as a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation (HSCT) to minimize remaining tumor cells at the time of transplantation. Achieving an undetectable number of remaining tumor cells is key to the outcome of allogeneic HSCT. For this purpose, CAR-T therapy was developed. Initially, using viral genes for gene construct transfection and targeting the CD19 antigen, which is also expressed on normal cells, was considered acceptable because subsequent conditioning treatment for allo HSCT would eliminate all CAR-T cells. However, when companies involved in the development of CAR-T therapy aimed to develop it as a standalone therapy rather than in combination with allo HSCT, issues such as the risk of viral genes and the destruction of CD19-expressing normal B cells emerged. Recently, reports have surfaced regarding secondary T-cell malignancies after CAR-T therapy. Both retrovirus and lentivirus, which are used in CAR-T therapy today, have been associated with T-cell malignancies.

Questions have arisen regarding the gene construct, specifically whether CD28 or 4.1BB is superior. Japanese experiences have shown that the CD28 construct is more potent than the 4.1BB construct. Additionally, some groups have reported that CAR-T treatment followed by allo HSCT results in significantly better survival rates than CAR-T therapy alone.

Pricing is another significant issue in CAR-T therapy. Novartis introduced CAR-T technology from the University of Pennsylvania, although the university itself obtained the technology from St. Jude Children's Hospital. St. Jude licensed its technology to Juno, leading to a patent dispute when Novartis infringed on Juno's patent rights. Novartis eventually made a substantial down payment and promised royalty payments, allowing them to charge exorbitant prices for CAR-T therapy. Other companies followed suit in pricing.

2. To address the potential risks associated with viral genes, a Japanese group developed the transposon method known as the 'PiggyBac Method'. This method transfers the CAR gene into T-cells without the need for viral genes, thereby eliminating the expense and special handling requirements associated with viral genes. The transduction efficiency of this method is comparable to that of viral gene transduction. The key element lies in electroporation

technology. A Chinese company has developed an affordable electroporation system capable of processing larger volumes at one time, further reducing the risk associated with viral genes. Transposon-derived CAR-T cells are much more cost-effective than virus-derived CAR-T cells, depending on the therapy.

3. For activating antigen-specific immune responses, dendritic cells (DCs) represent a superior method. The immune reaction involves a comprehensive system comprising not only T-cells but also NK cells, NKT cells, macrophages, and neutrophils. DCs play a crucial role in transferring immune response signals to all immune cells. DC-derived exosomes can be utilized for immune signal transfer, allowing for the loading of multiple antigens simultaneously. This approach can elicit a more potent immune response against the target by engaging all immune-related cells, not just T-cells. Studies have shown promising results using DC-derived exosomes for cancer treatment to induce immune responses.

4. Multiple myeloma can be treated with high-dose chemotherapy followed by autologous HSCT. Recently, the US FDA approved autologous HSCT for multiple myeloma treatment, marking an important regulatory milestone. However, there is a need for a system to approve therapies officially and enable reimbursement through public insurance. Treatment authorization may vary on a hospital-by-hospital basis. Although high-dose chemotherapy followed by autologous HSCT combined with DC therapy has shown improved survival rates, there is currently no commercial product available due to the personalized nature of DC therapy. Despite the lack of commercial interest from companies, developing such unique therapies is crucial for patients. Hospitals have an opportunity to fill this gap by developing these therapies, presenting a potential business opportunity for companies to provide services to hospitals.

Summarized by Josephine D. Nanda, MD, PhD

THE NEW ERA FOR CELL AND GENE THERAPY

THE OPPORTUNITIES AND CHALLENGES

RITA Y.H. HUANG, EDITOR-IN-CHIEF, THE ACTO TIMES

2024 signifies a new chapter in the field of cell and gene therapy (CGT). The world is now in an era of rapid ageing and coexistence with viruses. However, the emergence of new diseases in this viral era and super-aging society poses challenges to the current healthcare system in meeting the prevailing needs. As a result, CGT has emerged as a new medical paradigm, focusing on cells, cell derivatives, genes, and tissue engineering. In response to these emerging medical needs, priority should be given to new medical regulations, clinical practices, medical subsidies (such as national and private health insurance), and the alignment of industry chains. These unmet needs in emerging healthcare present both new opportunities and challenges for the field of CGT in this new era.

Key Opportunities for the New CGT Era

Opportunity 1: The Global CGT Market is Thriving in Europe and North America leading in Gene and Allogeneic Cell Therapies, While the Asia Market is Growing Rapidly.

The latest data published by the Alliance for Regenerative Medicine (ARM) reveals a substantial decrease in overall funding. In 2023, funding reached a historic low of $6.6 billion, representing a 30% decline from the peak of $22.7 billion in 2021. This decline can be attributed to consecutive global health crises and inflationary factors. However, despite this decrease in funding, the number of global regenerative medicine developers continues to grow rapidly, going from 1,369 in 2022 to 2,575 in 2023, with Asia leading the growth trend.

Moreover, the number of CGT clinical trials has reached 2,000, and the scope of disease indications being covered has expanded beyond rare diseases, with a particular emphasis on gene therapy. In the past year, the United States and the European Union have taken a more open-minded approach to gene therapy and have implemented a "sandbox" strategy specifically for rare disease gene therapy. This policy allows for the exploration of gene-based treatments, including CRISPR gene editing and gene-based cell therapies like CAR-T, to address diseases with unmet medical needs. Currently, the FDA has approved nine gene therapies, all of which target rare genetic diseases, along with six CAR-T cell therapies approved for hematologic malignancies.

Opportunity 2: Rise of CGT with "Precision Medicine" Prototypes

The United States and the European Union are leading the way in actively developing allogeneic cell and gene therapies, which sets the trend for future markets. It is encouraging to see that CGT, which was in its early stages, is now showing prototypes of "precision medicine" by focusing on using the right cells for the right indications. Currently, gene therapy is primarily being used for rare diseases, with a practice resembling a medical sandbox. Alternatively, gene-modified immune cell therapy targets cancer treatment, while cell therapy is primarily aimed at addressing non-oncological chronic diseases and unmet medical needs.

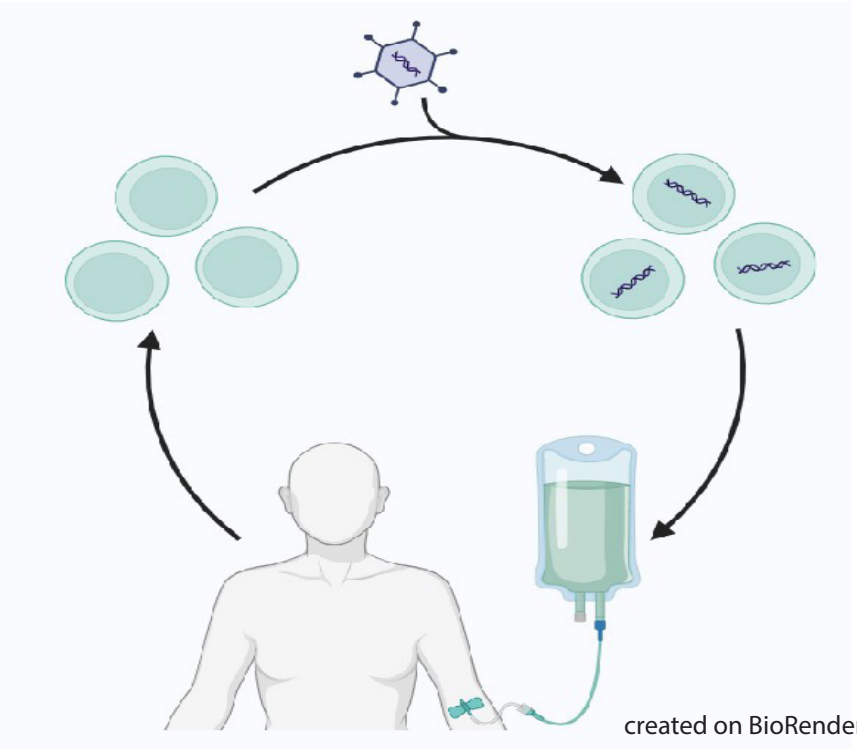
Looking ahead, gene or cell therapies that have completed phase III clinical trials are expected to be the first to enter the market. This aligns with the strategic emphasis on rare diseases, ageing-related conditions, and the post-pandemic era. The development of gene-modified cell therapies that target specific biomarkers for cancer treatment is

also highly anticipated in the future.

Opportunity 3: Exploring the Right to Try Law and Medical Sandbox

During President Trump's term, a significant initiative was the approval of the "Right to Try Law" by the United States House of Representatives in 2018. This law allows terminally ill patients to access treatments that have completed Phase 1 clinical trials but have not yet received FDA approval. These treatments include small molecule drugs, biologics, and medical devices. While the concept of this law is commendable, the availability of data on treatments accessed through it has been limited since its enactment. Drugs that are approved based on clear safety and efficacy data from clinical trials are still strongly recommended. However, it typically takes at least ten years for drug development, and specifically for CGT as an emerging therapy, clinical data is still scarce. Consequently, regulatory agencies tend to be more conservative in their approach.

Fortunately, in 2023, the U.S. FDA adopted a proactive and open-minded approach to reviewing treatments, particularly for medical needs such as rare diseases, aging-related conditions, and ineffective cancer treatments. The FDA implemented a medical sandbox strategy for regenerative medicine, providing medical opportunities to patients. A notable development is the FDA approval of Casgevy, a genetically modified cell therapy that utilizes CRISPR/Cas9 gene editing. This therapy has been approved for the treatment of hereditary sickle cell disease and transfusion-dependent beta-thalassemia (TDT) in December 2023 and January 2024 respectively. This brings renewed hope to patients with rare diseases who are in need of medical treatment. The FDA's focus on addressing medical needs and the utilization of the medical sandbox for CGT is commendable, as it accelerates the progress of this emerging therapy.



Challenges Faced by the Next CGT Generation

Challenge 1: Regulatory Incompleteness in Pharmacokinetics (PK) and Pharmacodynamics (PD) of the CGT

Traditional drugs typically have a single structure, high purity, and regulated dosage for specific message delivery within cells. Their pharmacokinetics (PK) describe the body's response through ADME factors: absorption (A), distribution (D), metabolism (M), and excretion (E). However, cells are distinct from traditional drugs as they are living organisms that exhibit diverse and dynamic responses depending on the tissue environment. They possess multiple action mechanisms during cell-tissue interactions, which significantly differ from the single-message delivery mechanism of traditional drugs.

While the US FDA has established regulatory guidance principles similar to small molecule drugs for CAR-T therapy, there is currently a lack of specific guidance for other cell types, such as non-targeted human stem cells, somatic cells, and immune cells. There is an ongoing discussion to elucidate the pharmacokinetics/pharmacodynamics (PK/PD) and mechanism of action (MOA) of cell therapies for disease treatment. This involves defining their safety and efficacy parameters and implementing effective regulation measures.

Challenge 2: High CGT Price and Insufficient Medical Subsidies

The issue of expensive CGT medications leading to limited accessibility to healthcare is well-known. It creates a dilemma where patients must balance their financial resources with their lives.

The high prices of CGT medications have emerged as a significant concern. For example, Hemgenix, a gene therapy for type B hemophilia developed by Australian pharmaceutical company CSL Behring, is priced at an astonishing $3.5 million USD. Zolgensma, a treatment for spinal muscular atrophy, costs $2.125 million USD. CAR-T therapy, approved in 2017, is priced between $375,000 to $470,000 USD. These exorbitant costs make it feasible for only a small number of patients to afford such treatments. Despite the promising potential of regenerative medicine, the issue of healthcare accessibility being centered around wealth remains a topic of debate.

Ensuring equal access to affordable healthcare is a fundamental value in the medical field. Countries promoting emerging CGT therapies have implemented measures to provide medical subsidies to patients through government healthcare insurance and private commercial insurance. For instance, in Japan, approved regenerative medicine products are included in the government's public insurance system to foster their development. They have also introduced "conditionally approved emerging cell and gene therapies," which can be partially covered by public insurance and complemented by private commercial insurance. South Korea has currently approved eighteen regenerative medicine products, with six of them receiving government subsidies through the public insurance program in collaboration with private insurers. In the United States, European Union, United Kingdom, South Korea, and the Netherlands, efforts have been made to include Zolgensma in national healthcare insurance or through partnerships with private insurance companies. Additionally, Medicare, the U.S. insurance program for older adults, provides coverage for cancer treatment drugs approved by the FDA. Although these healthcare initiatives hope to ensure equal opportunities for patients to access emerging therapies, there remains a pressing need for CGT medical subsidies for solid cancer patients and those beyond rare diseases. The issue of insufficient medical coverage for CGT remains significant and must be addressed and resolved in the next phase of CGT era.

Challenge 3: Talent Shortage

Regulations for CGT differ across countries, and there is a notable expertise gap, particularly in regulatory affairs. To address the growing number of clinical trial submissions, the US FDA has set up the Office of Therapeutic Products (OTP) and hired a hundred staff members to accelerate the review process. However, there is still a global challenge in the scarcity of skilled regulatory personnel, as there is a lack of expertise in the dynamic and complex field of living cell therapies.

CGT is a highly specialized industry that demands expertise in personalized and precision medicine. There is a significant demand for talent in scientific research, medical practice, and industry related to CGT. To tackle the shortage of talent, pioneering countries in regenerative medicine have implemented programs to cultivate skilled professionals. Renowned universities in the United States, for example, offer formal graduate programs and online courses specifically focused on regenerative medicine to cater to professionals from diverse backgrounds. The Japanese Society for Regenerative Medicine (JSRM) also offers training and certification programs for cell culture operators to ensure stringent quality control in cell-based therapies. These initiatives aim to address the talent gap and enhance the expertise in the field of CGT.

The priority lies in providing related professional training and certification courses for healthcare professionals such as physicians, pharmacists, medical laboratory technologists, and nurses. To advance precision CGT, it is crucial to establish talent development programs and offer on-the-job training alongside CGT-related courses. This should include foundational courses on cell therapy, regulations, clinical trials, medical ethics, and industry blockchain. Incorporating virtual reality (VR) and practical operation training for Good Tissue Practice (GTP) and PIC/S GMP in parallel clinical cell manufacturing is also essential.

Ultimately, the construction of a comprehensive "modular curriculum roadmap" and the implementation of different levels of "stackable credentials" will effectively drive talent progression. This approach will cater to individuals from diverse backgrounds and areas of expertise, ensuring a well-rounded training roadmap.

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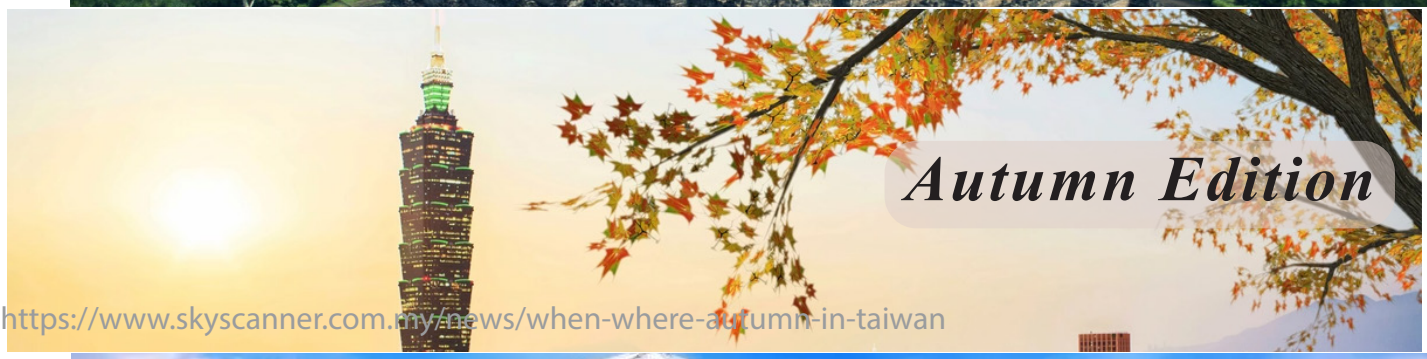

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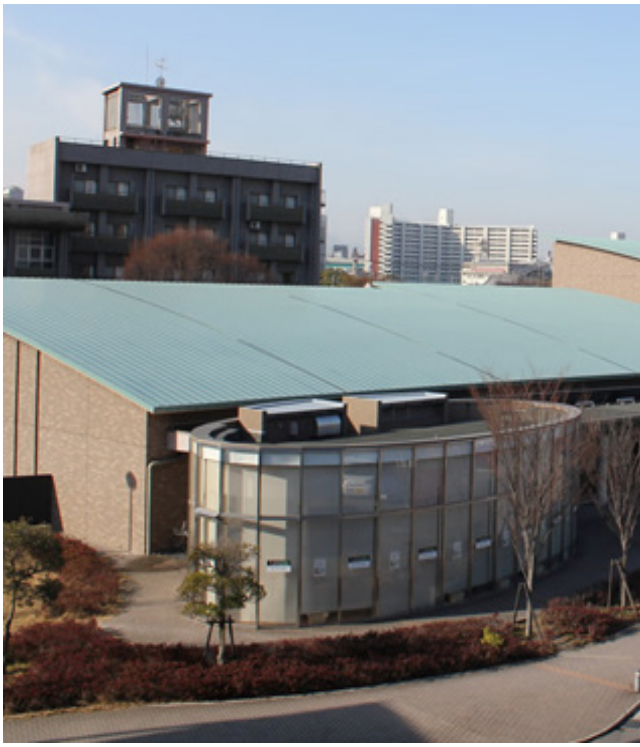
The annual gathering of the Asian Cellular Therapy Organization (ACTO) in Fukuoka, Japan, served as a momentous occasion. Against the backdrop of Fukuoka's rich cultural heritage and historical significance as a hub of cross-cultural exchange, renowned speakers from regulatory agencies across Asia, including representatives from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor and Welfare (MOHLW), convened to share vital updates on regulatory landscapes in their respective countries and regions.

With CAR-T therapy emerging as a focal point in the field of cellular therapy, expert speakers delved into various facets of this groundbreaking technology, offering insights into its diverse applications and advancements. Additionally, discussions on gene therapy, led by experts from Japan and Thailand, shed light on the latest clinical applications and developments in this rapidly evolving field.

The meeting also highlighted Japan's pioneering strides in regenerative therapy, showcasing treatments already approved as advanced therapies within the country. Furthermore, immune cell therapy, particularly NK cell therapy, emerged as a vital area of exploration, with discussions centered on diverse approaches and promising developments.



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MEETING
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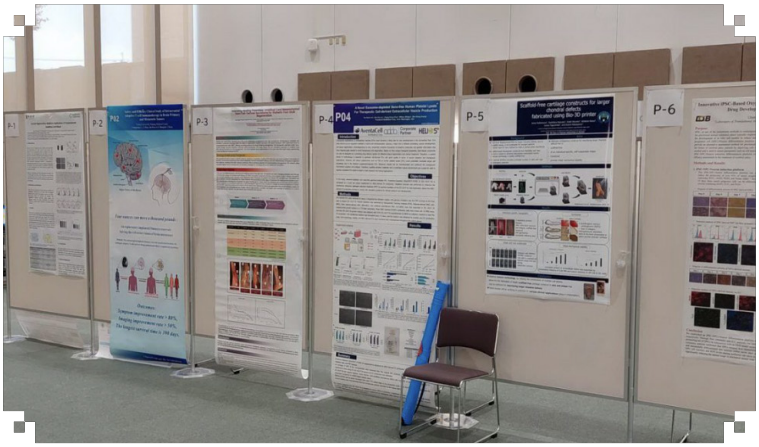
Technical sessions featuring presentations from leading technology companies provided attendees with a glimpse into cutting-edge innovations poised to reshape the landscape of cellular therapy. Moreover, the vice presidents of ACTO from each Asian country reported on updated information regarding cellular therapy within their respective regions, emphasizing the importance of collaborative efforts among academia, industry, and regulatory agencies in driving innovation and advancing therapeutic development.

Founded in 2010 as the ISCT Asian Regional Meeting, ACTO has evolved into a dynamic organization dedicated to facilitating research and development in cellular therapy while fostering collaboration among key stakeholders. Through its commitment to accessibility, with registration fees substantially lower than international standards, ACTO continues to democratize scientific discourse and support the advancement of cellular therapy in Asia and beyond.

As attendees departed Fukuoka, they carried with them not only a wealth of knowledge and insights gained from the meeting but also a renewed sense of purpose and determination to further propel the field of cellular therapy towards unprecedented heights of innovation and impact.

Summarized by Nova Yuli Prasetyo Budi, MD



REPORT

ADVANCES IN CAR-T DEVELOPMENT

November 6, 2023

Session Chair: Takanori Teshima, Hokkaido University, Japan

Summarized by Josephine Diony Nanda, MD, PhD

This session will address key topics in cellular therapy, including CD19-directed CAR-T for B-cell lymphomas, PiggyBac transposon-mediated CAR-T therapy, novel CD20 and CD19 targeting tandem CARs, CD7 CAR-T therapy for T cell malignancies, allogeneic CAR-T cells for hematological malignancies, and real-world data on tisagenlecleucel in Japanese diffuse large B-cell lymphoma patients.

Dr. Linda Hanssens, Miltenyi Biomedicine, Germany

Tandem CAR-T targeting CD19 and CD20 are developed to reduce the risk of antigen escape and subsequent relapse in the single target. A preclinical study of autologous pLTG1497-transduced CAR T-cells (lentiviral transducted MB-CART2019.1) in r/r B-NHL patients showed improved anti-lymphoma efficacy. Further evaluation of effectiveness and safety MB-CART2019.1 in adult patients with CD20 and CD 19 positive r/r DLBCL showed no DLT, and no severe (grade ≥3) CRS or neurotoxicity was observed, even in the elderly. All six patients treated on DL2 responded and achieved CR and ongoing remission in due time. Further clinical phase II and phase II trial studies for relapsed aggressive B-NHL patients are underway.

Prof. Yoshiyuki Takahashi, Nagoya, Japan

To reduce the manufacturing cost of CAR-T, a method of CAR-T production using a non-viral gene transfer, piggyBac transposon, was proposed. With smaller scale cell culture facilities to produce a significant quantity of vectors needed, Autologous T-cells via the piggyBac transposon system with CD19 incorporation with CD28 costimulatory domain were developed and further checked in the clinical trial for CD19 positive ALL patients. A single-dose injection was given to all patients after lymphodepletion using Fludarabine and Cyclophosphamide. The first clinical trial in Japan showed no dose-limiting toxicities (DLT), two CRS grades 1 and 2, and only one neurological event was observed. However, hematological toxicity grade 3 or 4 was found in all patients. Four out of six patients obtained CR during the observation period (10 - 36 months). Further trials in Thailand's first patient, a relapsed and chemotherapy-resistant malignant melanoma patient, showed disease-free one-year post-CAR-T treatment. This method continued to develop in Japan, targeting ALL, NHL, GD2 positive tumors, AML, HER2 positive tumors and soft tissue tumors.

Dr. Koji Izutsu, Tokyo, Japan

Four CAR-T therapies for relapsed/refractory B-cell lymphoma were approved globally, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). Three were accepted for DLBCL in Japan at the third or later line (3L+) based on single-arm phase 2 studies. Namely tisagenlecleucel (tisa-cel) in March 2019 for 3L+ DLBCL and FL in August 2022, axicabtagene ciloleucel (axi-cel) for 3L+ DLBCL in January 2021, also for transplant-eligible high-risk patients with 2L DLBCL, and lisocabtagene maraleucel (liso-cel) for 3L+ DLBCL in March 2021 and 2L DLBCL in December 2022. Although the approval of various CAR-T products in Japan has been done, it's still far from the total involvement in the clinical practice as some infrastructure and capable human source issues are still found.

Dr. Hideki Goto, Hokkaido, Japan

Around a quarter of diffuse large B-cell lymphoma (DLBCL) patients would relapse even after a successful primary immunotherapy with either R-CHOP or Pola-R-CHP. Tisagenlecleucel (tisa-cel), a second generation of autologous anti-CD19 CAR-T therapy, might offer some hope as the global reported 61.8% response rate, with 12 months PFS at 26.4% and OS 56.3%. A retrospective multicentre study was performed on r/r DLBCL and r/r transformed follicular lymphoma (tFL) patients from October 2019 to October 2021 (SETUP study). Eighty-nine patients were recruited, and 73% achieved clinical response (CR at 55% and PR at 18%), with six months OS at 76.6% and EFS at 54%. After a year, OS was 67%, and EFS was 46.3%. Multivariate analysis showed that high metabolic tumor value (MTV ≥ 80ml) and stable/progressive disease before infusion was associated with poor EFS and OS.

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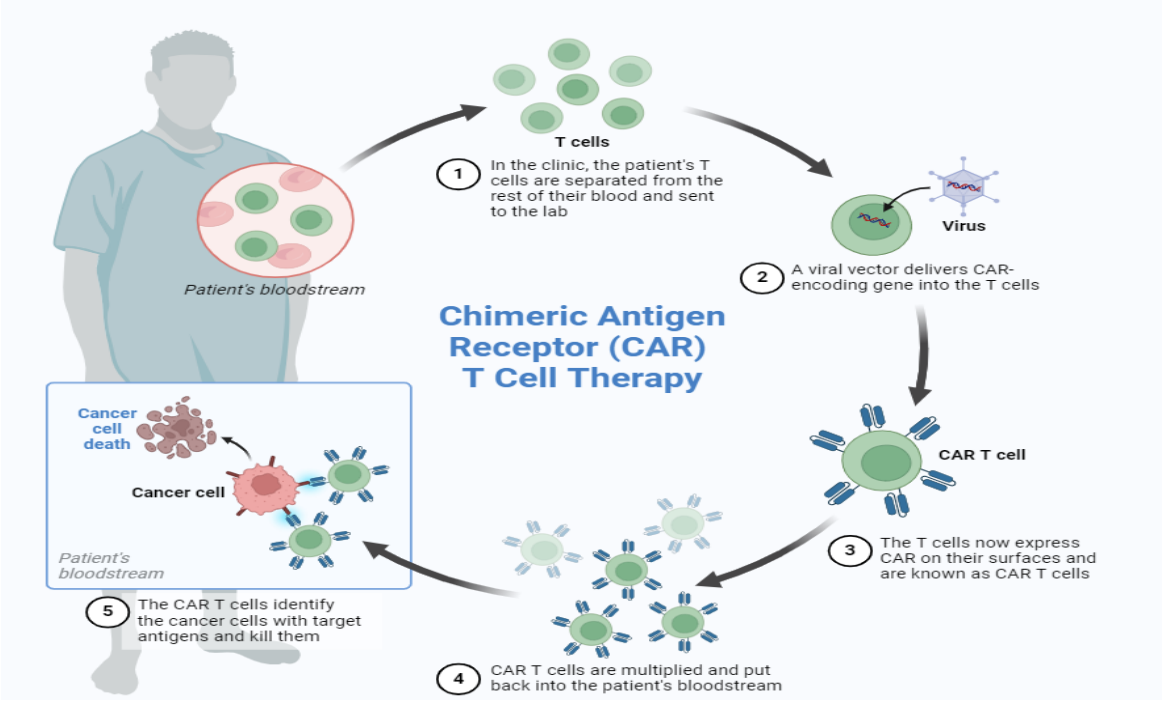
Dr. Yu Yagi, Tokyo, Japan

> These genetically engineered cells navigate the intricate terrain of precision medicine, deploying their customized receptors to dismantle the molecular intricacies of disease, rewriting the code of therapeutic achievement at the cellular level.

Anti-CD19 CAR-T has shown impressive results in patients with r/r large B-cell lymphoma (LBCL) who have failed two or more lines of treatment in a single-arm phase-two trial. The global report of axi-cel, one of the FDA-accepted CAR-T, showed 35-40% success after five years of trial. However, this treatment still poses some side effects to the patients: cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome, prolonged cytopenia, B-cell aplasia, and some complications caused by infections. As it recently entered the clinical practice, several differences might be found, as in patient characteristics, differences in vein-to-vein intervals, the necessity to holding cytoreductive therapy between injection and leukapheresis, or bridging between leukapheresis and infusion therapy.



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Some regional factors and center-specific differences in referral patterns and eligibility criteria might also influence access to CAR-T cell therapy. Observed variability was observed in chemosensitivity evaluation before autologous stem cell transplantation (auto-HSCT) or the selection of particular condition patients (advanced age and comorbidity). Other region-based differences were found in waiting time for indication, leukapheresis, and manufacturing slots, which might contribute to survival outcomes. Several disease and patient-specific factors have been associated with poor outcomes after CAR-T infusion. This could optimize the patient selection and treatment process to enhance their benefit despite its high costs and limited access.

Recent updates on CAR-T cell distribution in Japan: As of April 2023, 42 centers are performing CAR-T cell therapy to r/r LBCL patients who failed at least two lines of chemotherapy. The majority of patients receive bridging treatment, and even though the practice patterns varied from the clinical trial, its outcomes were comparable to clinical trials and other reports from the US and Europe.

Prof. Yongxian Hu, Hangzhou, China

As the significant challenges of autologous CART might hinder the reach and effectiveness of the therapy, modified allogenic CAR-T might provide the solution. The clinical trial of GC007g, an allogenic human HLA-matched, donor-derived, CD19 targeted CAR-T cell therapy, for r/r B-ALL showed low CRS and aGvHD incidence with a year PFS 76.2% and OS 85.7%. This CD19 CART is also designed for those who relapsed after receiving an allogeneic human stem cell transplant (allo-HSCT) and might not be eligible to receive autologous CAR-T therapy due to poor cell condition, infection and other factors. Another cell developed, CTA101, was the first generation of Universal CAR-T, equipped with a "suicide switch" -RQR8 and underwent CRISPR/Cas9 to knock out the TRAC locus and CD52 to prevent host immune rejection. Six patients recruited were injected with a single dose of CTA101 from two different donors (two recipient groups) post-chemotherapy pretreatment. All recipients developed CRS, with only one over grade three, no GvHD and no detectable inverse replication-competent lentivirus (RCL) recorded. At day 28 post-injection, 83.3% of patients archived CR/Cri and MRD negative; on the follow-up (2-8 months), only three remained. As CD52 monoclonal antibodies have some side effects, the second-generation universal CAR-T cells were developed using a non-gene-editing membrane protein intercellular retention platform to achieve a similar effect as the previous generation. Testing on r/r patients with 75% concomitant lymph node invasion and 12.5% post-autologous CD19 and CD20 relapse showed no over-grade 3 CRS and no GvHD observed.

However, two patients developed reversible HLH, shown as lymphocytopenia and neutropenia. Efficacy was not obtained from two patients; the rest showed a 100% ORR rate (83.3% CR, 16.7% PR, with one CR of more than a year). Another universal CAR-T targeting CD19, SC-U02, underwent TCR and B2M gene knock-out to avoid GvHD and T-cell rejection, cochimerized with B2M-HLA-E to avoid NK-cell rejection. It was tested on two patients with relapsed refractory r/r DLBCL and showed only one PR. In the second part of the talk, using CAR-T cells to treat T-cell hematological malignancies poses some risk of fratricide, aplasia and contamination of the product. So, the design involved CD7 knockout to avoid fratricide, with TCR and HLA knockout to prevent GvHD and T-cell rejection, respectively. NK-inhibitory receptors (E-cadherin) were added to avoid host NK-cell activation after HLA knockout. This was proven in the ex-vivo and in vitro studies followed by a single arm, 3+3 design, dose-escalation phase 1 clinical trial. Eleven T-ALL/NHL and one AML patient were enrolled; however, after the safety analysis, one patient died due to sepsis before efficacy analysis. All patients received fludarabine, cyclophosphamide, and etoposide conditioning with RD13-01 infusion. No DLT, GvHD or ICANS were observed; serum IFN-ɣ, IL-6 and IL-10 were correlated with CRS status; EBV (n = 4) and CMV (n = 2) reactivation were found. The result showed 85% reached OR, 75% CR/CRi (three lymphoma patients underwent OR, 1 CR; disease progression in three leukemia and one with lymphoma; one developed EBV-associated DLBCL and passed away on day 93 post-injection; three months post-injection three patients were bridged to allo-SCT were in continuous remission). In the last part, iPSC-derived CAR macrophages were made capable of causing antigen-dependent phagocytosis and lysis of tumor cells, which has already been proven in the animal model with high anti-tumor efficacy.

Dr. Peggy Lu, Beijing, China

A phase I/II clinical trial for pediatric and adult r/r T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma (T-ALL/LBL) patients were treated with a single dose of naturally selected anti-CD7 CAR (NS7CAR). Dosages were grouped into low, medium and high, and the post-treatment results showed bone marrow deep CR on 94.4% of patients recruited. Patients with extramedullary disease (EMD) showed 56% CR and 22% PR (partial response) within follow-up time (22-833 days, median 368.5 days). Pediatric or adult patients and varied doses showed no considerable difference between two-year overall survival (OS) and progression-free survival (PFS). Between CR patients, PFS was significantly higher in those who proceeded with consolidation allo-HSCT, as the majority of those who didn't relapse within 150 days. Cytokine release syndrome (CRS) was reported in 91.7% of patients (grade 1/2 80%, grade 3/4 11.7%) and 5% neurotoxicity.

IMMUNE CELL THERAPY UPDATES

November 6, 2023

Safety Evaluation Of Immune Cell Therapy For Malignant Tumor In Cancer Immune Cell Therapy Evaluation Group (CITEG)

Summarized by Ageng Brahmadhi, PhD

The SETA Clinic Group was founded in 1999 as a specialized clinic focusing on Immuno-Cell Therapy for cancer patients. This group collaborates with 33 medical institutions in Japan to offer treatment to cancer patients. They specialize in immune cell therapy (ICT) utilizing a variety of cells, an approach they refer to as the individualization of ICT.

As we are aware, cancer cells exhibit various mutations and express multiple cancer antigens on their cell membranes. Dendritic cells (DCs) play a crucial role in presenting antigens to T cells and eradicating cancer cells, a process known as antigen-specific acquired immune response. Additionally, a non-specific innate immune response, involving NK cells and Gamma dendritic cells, contributes to the defense against cancer cells.

At present, SETA Clinic offers effector cell therapies such as αβ T cell therapy, γδ T cell therapy, NK cell therapy, and NKT cell therapy. They also provide cell vaccines, including dendritic cell vaccines, oncoantigens, and neoantigen-pulsed vaccines.

Between 1999 and 2022, over 20,000 patients have been treated, totaling approximately 190,000 treatments. In 2015, the Cancer Immune Cell Therapy Evaluation Group (CITEG) was established, concluding that immune-cell therapy for cancer is a safe treatment option.

The prospective CITEG clinical study conducted from 2015 to 2022 focused on αβ T cell therapy, γδ T cell therapy, NK cell therapy, and DC therapy for malignant tumors. The study included patients aged ≥64 years old (52%) and <64 years old (47.8%), with a nearly equal distribution between females and males. The majority of cancer cases were in advanced stages (84%), with a performance status (PS zero) of 66.5%. The top five primary cancer diagnoses were pancreas, colorectal, lung, stomach, and breast cancers. Interestingly, no significant differences in the occurrence of adverse events were observed based on tumor types.

The overall incidence rate of adverse events (AE) associated with immune cell therapy was 3%. When categorized by the type of immune cell therapy, the incidence of AEs for αβ T cell therapy was 1.8%, γδ T cell therapy was 1.1%, NK cell therapy was 1.6%, and DC therapy was 5.4%. Notably, the incidence of AEs in DC therapy was higher compared to other types of cell therapy, and αβ T cell therapy exhibited more AEs compared to γδ T cell therapy.

A significant proportion of AEs occurred within 2 days after treatment in over 95% of patients. Specifically, for αβ T cell therapy, γδ T cell therapy, and NK cell therapy, AEs occurred after 3-4 administrations, whereas for DC therapy, AEs were observed after the 5th administration.

In patients undergoing αβ T cell therapy, the risk of adverse events (AE) was higher in those with a performance status (PS) of 1 or higher. Conversely, the incidence of AEs decreased when immune cell therapy was combined with molecular targeting therapy and endocrine therapy.

For patients receiving DC therapy, age and combination therapy were identified as risk factors. Younger females (<64 years old) undergoing adjuvant therapy had a higher risk of AEs, whereas the risk was lower when combined with surgery or surgery in conjunction with chemotherapy. Notably, three cases experienced serious AEs necessitating hospitalization.

Currently, they are conducting safety studies on cell therapy in combination with immune checkpoint inhibitors. In their case report paper, they indicated the potential to enhance immune checkpoint inhibitors by boosting immune function through cell therapy. In conclusion, immune cell therapy for cancer is deemed safe, with no reported serious adverse events.

REPORT

ASIA CELL & GENE THERAPY REGULATION

November 7, 2023

Unlocking the Future: Cell and Gene Therapy in Asia

ROUND TABLE DISCUSSION

The key objective of the ACTO roundtable session is to facilitate extensive communication among various countries, particularly focusing on regulatory harmonization and the development of CGT products. Experts from Japan, Singapore, Taiwan, Indonesia, and Korea participated in this discussion session.

During this session, the discussion primarily revolved around two key questions. The first question addressed the scenario where a foreign academic institution or company intends to develop cell and gene therapy products in a specific country. The second question delved into providing advice to cell and gene therapy investigators or sponsors in light of the first question.

As anticipated, experts provided varied responses concerning the policies implemented in their respective countries. Nevertheless, a common thread emerged across these countries concerning the fundamental licensing procedures. All experts recommended that, prior to establishing a cell-based therapy business in their respective countries, companies should engage with the relevant authorities to obtain the necessary permissions, regulatory guidance, and requirements. Additionally, it was advised that companies should outline their plans for application and business expansion in the future during these discussions.

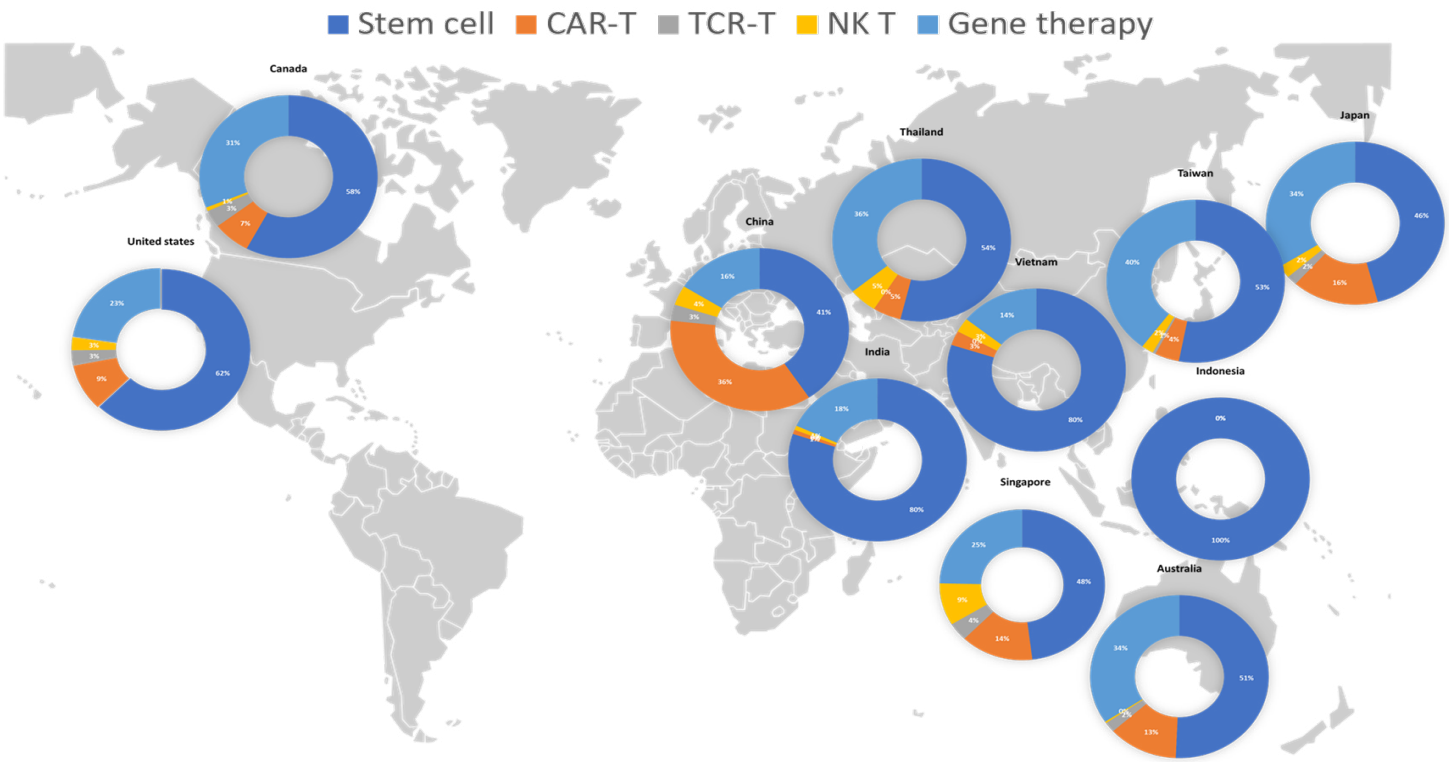
The company should take into account the potential variations in requirements for regulatory approval, as well as the Chemistry, Manufacturing, and Controls (CMC) for both non-clinical and clinical necessities. For instance, in Japan, companies are mandated to furnish clinical data on safety and efficacy, even for small-scale clinical trials. There is an accelerated pathway available for subsequent applications, expediting the application and assessment processes. In Singapore, CMC considerations encompass product quality specifications, product identity, purity, crucial potency test results, and mechanism of action reports. Moreover, Singapore places a significant emphasis on donor eligibility, necessitating new eligibility approval even for products deemed eligible in other countries.

In Taiwan, companies aiming to introduce their products must provide comprehensive information regarding the manufacturing process, clinical trial protocols, acceptance criteria, and specify the source conditions. Additional requirements in Indonesia and Korea include article submissions, with Indonesia mandating information on product toxicity and result consistency. Korea requires companies to classify their products accordingly.

Summarized by Ageng Brahmadhi, PhD

JAPAN

Regulations governing regenerative medicine for human use, including cell and gene therapy (CGT), have significantly evolved in Japan, aligning with advancements in clinical experience, scientific knowledge, and societal acceptance of these innovative technologies. In November 2014, Japan introduced two pivotal acts: “The Act on the Safety of Regenerative Medicine” (ASRM) and the “Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act” (PMD Act).



Current Cell and Gene Therapy Clinical Trials Map

clinicaltrials.gov

Under ASRM, medical institutions are entrusted with responsibilities to ensure the safety and transparency of regenerative medicine technologies. This act delineates the obligations and standards for medical facilities engaged in the application of CGT products, emphasizing patient safety and ethical considerations.

In addition to ASRM, the PMD Act introduced a new scheme that enables the conditional and time-limited approval of CGT products. This regulatory framework facilitates expedited access to pioneering therapies while upholding rigorous safety and efficacy standards. It offers a route to accelerate the introduction of promising CGT products to the market, benefiting patients in need of advanced medical interventions. The regulatory landscape in Japan continues to evolve to support the progress of research and development in CGT, with particular emphasis on gene therapy products. These advancements aim to foster innovation, guaranteeing the prompt development of safe and effective CGT solutions tailored to the specific needs of Japanese patients.

Overall, Japan's legislative frameworks embody a proactive stance toward regulating CGT, fostering innovation while prioritizing patient safety and ethical considerations. Through these initiatives, Japan seeks to establish itself at the forefront of global advancements in regenerative medicine and gene therapy.

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Summarized by Nova Yuli Prasetyo Budi, MD

TAIWAN

By Yueh-Tung Tsai

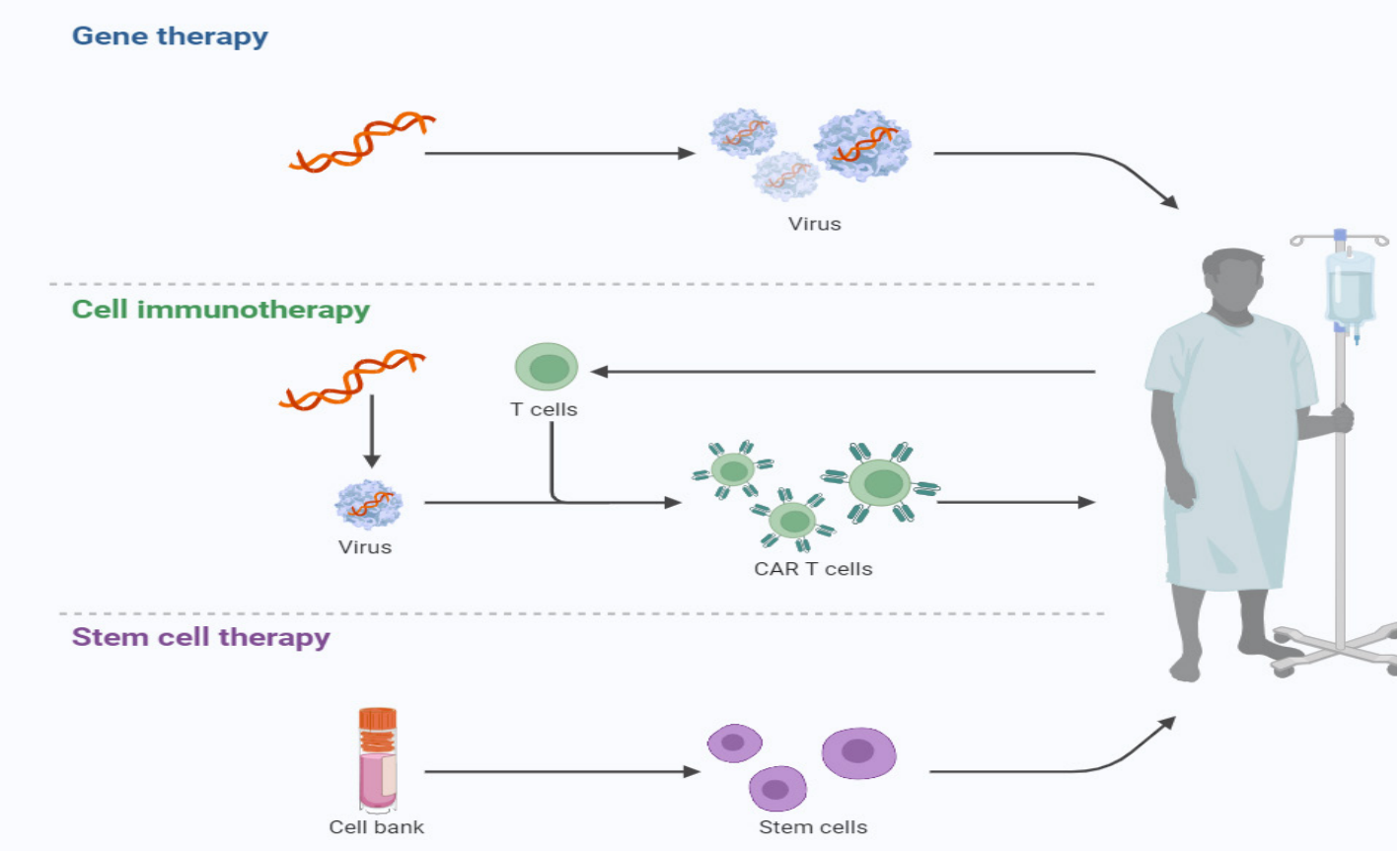
Taiwan's regenerative medicine regulation is aligned with that of the United States and Europe. To enhance patient access to cell-based therapies for innovative treatments, the Taiwan government implemented a dual-track regulation for cell-based therapeutic products in 2018. This framework comprises the "Regulation

Governing the Application of Specific Medical Examination Technique and Medical Device" (RASMET), also known as the "Special Regulation for Cell Therapy" under the Medical Care Act, and the "Regenerative Medicinal Product Management Act" solely under the Pharmaceutical Affairs Act. These regulations jointly promote the advancement of regenerative medicine.

The "Special Regulation for Cell Therapy" aims to oversee the use of cell-based therapy as a medical practice technique to foster clinical innovation across approved medical institutions for patients with specific medical indications. Under this regulation, the Ministry of Health and Welfare (MOHW) has approved six types of autologous cell-based therapies, classified as low risk due to their anticipated efficacy and established safety profiles for particular indications. These therapies, including autologous CD34+ cells, non-genetically modified immune cells (ex: late-stage cancer therapy), mesenchymal stem cells derived from bone marrow (ex: spinal cord injury) or adipose tissues (ex: arthritis and difficult wounds), and somatic fibroblast cells (ex: wound and wrinkle), do not necessitate Investigational New Drug (IND) application for market approval. To date, over 1400 patients have undergone autologous cell-based therapy under the "Special Regulation for Cell Therapy," with immune cell cancer therapy comprising approximately 90% of these cases. The efficacy of mesenchymal stem cell therapy for osteoarthritis is promising.

Nevertheless, cell-based therapy products derived from autologous sources not listed in the approved catalogue must provide clinical evidence before gaining approval. To address this, the MOHW has established and empowered two review committee board to supervise the use of these cell-based therapy technologies in medical practice. One committee board evaluates proposals focusing on the scientific foundation and treatment plan of specific cell-based therapy products, while the other board assesses the consumer pricing of the treatments. Each committee comprises experts from academic research, clinical, statistical, legal, insurance, and bioethics backgrounds.

Additionally, the pending "Regenerative Medicinal Product Act" is designed to regulate regenerative products,



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encompassing high-risk products like cells, cellular derivatives (such as EVs), genes, and medical devices (combinations of cells and devices). The Taiwan Food and Drug Administration (TFDA) serves as the regulatory authority overseeing the manufacturing of regenerative products under Good Manufacturing Practice (GMP) standards and the execution of clinical trials for such products, while the Center for Drug Evaluation (CDE) provides advisory consultations and aids in the review process of medicinal products.

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CHINA

China regulates Advanced Therapy Medicinal Products (ATMPs), including gene therapy, cell therapy, tissue-engineered products, etc., under the classification of "innovative biological products." The National Medical Products Administration (NMPA) oversees their approval and regulation. By 2022, China had approved two CAR-T cell therapy products for specific lymphomas, with additional approvals anticipated. Expedited regulatory pathways like Priority Review and Breakthrough Therapy Designation have been implemented for fast-track ATMP approvals.

The regulatory framework has been optimized to streamline the drug review process, with NMPA striving to finalize New Drug Application (NDA) reviews within 200 days, or 130 days for ATMPs with Priority Review. Pre-IND meetings have become standard practice to verify data support for clinical trials, and advisory committee meetings are convened as needed to align stakeholders.

Technical guidance documents have been released by the Center for Drug Evaluation (CDE), detailing regulatory considerations for various ATMP categories, such as gene therapy and cell therapy products. China's participation in the International Conference on Harmonization (ICH) promotes international collaboration on ATMP regulation.

The number of ATMP Investigational New Drug (IND) applications has surged since 2017, with immune cell products and stem cell products being the most frequently submitted types. Oncolytic viruses, in vivo gene therapy products, and other varieties have also been submitted. Despite challenges such as limited characterization and complex comparability studies, China aims to strengthen its regulatory framework for ATMPs to to adequately address unmet medical requirements.

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Summarized by Nova Yuli Prasetyo Budi, MD

INDONESIA

By Rusdy Ghozali, MD, PhD

Indonesia currently lacks approval for any single-cell therapy product, despite the presence of numerous clinics offering stem cell treatments. According to Rasko et al. (2016), Indonesia ranks 10th globally in the number of stem cell clinics, a surprising fact given the absence of approved stem cell therapies.

Regulation and oversight of cell-based medicine in Indonesia involve three government agencies: the Ministry of Health (MOH), the Indonesia Food and Drug Agency (BPOM), and the National Research and Innovation Agency (BRIN). Unfortunately, there is overlap and unclear delineation of roles among these agencies, leading to conflicting regulations.

Several regulations have been issued, such as MOH Regulation no. 32 (2018) on stem cell and cell therapy

MOH regulation	BPOM regulation
• Cell therapy products must be produced in the lab certified by MoH. • The production facility can be a drug company, healthcare facility, or universities. • The laboratory must comply	• Cell therapy products can only be produced in the lab certified by BPOM (GMP certification). • The mass product production can only be performed by drug company. • The laboratory must have

services and BPOM Regulation no. 18 (2020) on the assessment of human cell-based medicines. However, this regulation overlaps with MOH regulation and need further confirmation to function properly.

Due to these conflicting regulations and strict oversight, only 14 legal hospitals are currently conducting cell-based therapy trials. Including, Dr Cipto Mangunkusumo hospital Jakarta, Dr Sutomo Hospital Surabaya, Dr M Djamil Padang, Harapan Kita National Cardiac Hospital Jakarta, Dharmais National Cancer Hospital Jakarta, Persahabatan Hospital Jakarta, Dr Hasan Sadikin Hospital Bandung, Dr Kariadi Hospital Semarang, Gatot Subroto National Army Hospital Jakarta, Dr Sardjito Hospital Yogyakarta, Prof Dr IGNG Ngoreah Hospital Bali, Dr Wahidin Sudirohusodo Hospital Makassar, Dr Moewardi Hospital Surakarta, Prof Mahas Mardjono National Brain Center Jakarta. Additionally, there are only 10 licensed laboratories approved by MOH for cell production, with two approved by the Indonesian FDA and 20 institutions seeking BPOM assistance for licensing.

Unlike the US, EU, and JAPAC countries with specific regulatory frameworks for cell-based medicines, Indonesia treats them as pharmaceutical products, lacking specific approval pathways for cell and gene therapies. Recognizing this issue, the Indonesian government is working on the Pentahelix system and developing an ecosystem for human cell and tissue-based medicines, involving government, academia, business, community, and media to address challenges and enhance the cell therapy industry and regulations.

Summarized by
Josephine D. Nanda, MD, PhD

VIETNAM

Cell and gene therapy products (CGT) have emerged as promising treatments for many diseases. Following the successful treatment of the first three cases with hematopoietic stem cell transplantation (HSCT) at the Blood Transfusion and Hematology Hospital in Ho Chi Minh City, Vietnam in 1995, there has been a significant focus on research and clinical trials involving CGT-based treatments.

Currently, some indications have been approved for CGT therapy by the Ministry of Health in Vietnam, including malignant hematologic diseases (such as multiple myeloma, Hodgkin or non-Hodgkin lymphoma, and acute lymphoblastic leukemia), chronic obstructive pulmonary disease (COPD), knee osteoarthritis, and spinal cord injury. Additionally, other successful applications of stem cell therapy have been reported in wound healing (such as burns, Steven Johnson syndrome), ulcers, autism, and more. Notably, in 2023, the Vinmec Research Institute of Stem Cell and Gene Technology in Vietnam reported the successful treatment of a 4-year-old acute lymphoblastic leukemia case with CAR-T cell therapy. Furthermore, there have been various studies exploring the application of gene therapy in conditions like Duchenne muscular dystrophy, Sickle cell anemia, and Thalassemia.

The regulatory framework governing the application of CGT treatment in clinical practice and on the market in Vietnam is primarily based on several key laws and regulations. These include the Law on Pharmacy (No. 105/2016/QH13), the Law on donation, removal, and transplantation of human tissues and organs (No. 75/2006/QH11), the Law on medical examination and treatment (No. 75/2006/QH11), among others. Various regulations have been enacted to oversee and manage CGT therapy, such as the Law on Quality of drugs and drug materials (No. 11/2018/TT-BYT), Regulation on incentive certification verification of projects for manufacturing in Vietnam (No. 55/2015/TT-BYT), Regulations on Drugs Subject to Bioequivalence Testing and Requirements for Records and Reports on Bioequivalence Research Data (No. 07/2022/TT-BYT), Regulations for Clinical Trials on Drugs (No. 29/2018/TT-BYT), and Bioequivalence Testing of Drugs (No. 10/2020/TT-BYT).

Furthermore, the Ministry of Health provides guidance on the application of CGT treatment, including specific details on indications, administration routes, dosages, and follow-up procedures for therapies like autologous and allogeneic HSCT and cell therapies such as CAR-T cell therapy in malignant hematologic diseases. For instance, detailed guidance can be found in the "Guidance for diagnosis and treatment of malignant hematologic diseases" (No. 1832/QĐ-BYT) issued in 2022. There are also guidelines outlining the application of cell therapy in various osteoarthropathy disorders within the "Guidance on the diagnosis and treatment of osteoarthropathy."

Lastly, to support and streamline research efforts in the field of CGT, guidance for the research of cell and cell-derived products in Vietnam was released in 2020.

Despite facing resource limitations and challenges, Viet Nam has seen significant progress in CGT treatment. Noteworthy achievements have been reported, accompanied by the emergence of advanced facilities with high-quality standards. Additionally, numerous research studies and clinical trials have been carried out, guided by ongoing advancements and improvements in the regulatory framework for CGT therapy.

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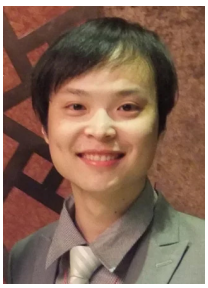

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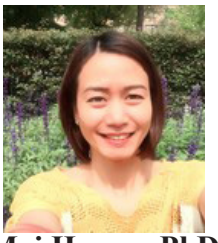

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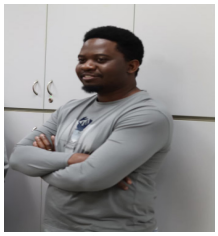

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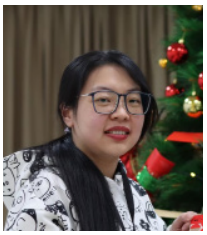

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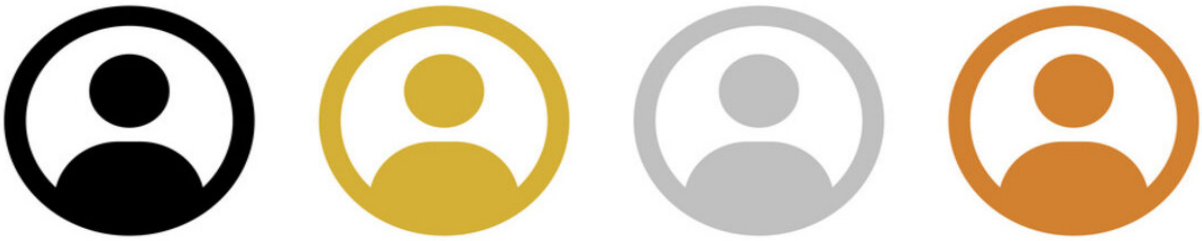

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