The ACTO Times

Asian Cellular Therapy Organization

Summer Edition

New Taiwan RM Regulations
Indonesia Spotlight and Halal Certification
2024 ISCT Report

Greeting

ACTO Chairperson

Dear ACTO members,

I am delighted to announce the release of The ACTO Times Summer Edition 2024. Following the success and appreciation of our inaugural Spring Edition, we are excited to continue advancing the field of cellular therapy in Asia. This edition comes at a particularly auspicious time as we celebrate a significant milestone in our field.

We are particularly thrilled to highlight and congratulate the recent regulatory advancements in Taiwan, where new regulations on regenerative medicine have been implemented. This progressive move by Taiwan's health authorities will undoubtedly pave the way for accelerated innovation and patient access to cell therapies. These regulations mark a significant step forward in our collective mission to enhance patient care through advanced medical technologies.

ACTO, founded in 2010, was created to address the unique challenges in our region. Over the years, we have grown into a vibrant community of professionals dedicated to pushing the boundaries of cell and gene therapy. The ACTO Times serves as a vital resource, providing insights into the latest research, clinical trials, product developments, and regulatory updates in cell and gene therapy.

Special thanks to Prof. Rita Yen-Hua Huang, our Editor-in-Chief, and all contributors for their dedication. Your hard work and commitment to excellence are what make this publication a valuable resource for our members. Your feedback and participation are essential as we strive to improve our publication and better serve our community.

Warm regards,

Akihiro Shimosaka

Editorial Greeting

The ACTO Times Editor-in-Chief

Dear Readers and Contributors,

I am delighted to extend my warmest welcome to you to The ACTO Times, the esteemed publication of the Asian Cellular Therapy Organization (ACTO) since the Spring of 2024.

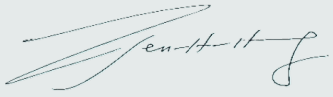
The ACTO Times serves as a platform for the global advancement of cell and gene therapy (CGT), with a particular focus on the Asian Pacific Area. Our goal is to facilitate the exchange of culture and knowledge, foster global connections encompassing education, regulation, clinical practice, and industry.

As the Editor-in-Chief, we unveiled the Spring Edition of The ACTO Times in April this year, which explored the history of ACTO and highlighted recent advancements in CGT, including immune cell therapy (CART and immune cells) and stem cell therapy (MSC, HSC), along with CGT regulations in Asian regions. The overwhelmingly positive feedback from our readers has been truly motivating.

I am excited to present the Summer Edition, which focuses on Halal Certification and Indonesia. Additionally, this edition includes a special report on Taiwan's new regulations for Regenerative Medicine approval, as well as coverage of the advancements and industry updates from the 2024 ISCT Annual Meeting.

I invite you once again to actively engage in The ACTO Times, share your expertise, contribute your discoveries, and participate in the vibrant discussions we strive to foster. I am looking forward to our collaboration in furthering The ACTO Times as a dynamic and influential platform for advancing cellular therapy in Asia and beyond.

Thank you for being a part of ACTO and The ACTO Times.



Rita YH Huang

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ACTO CHAIRMAN

Akihiro Shimosaka, Ph.D

The speech was delivered at Taiwan-Japan Joint Forum on Regenerative Therapy on June 6, 2024

Researchers are exploring innovative treatments for advanced non-small cell lung cancer (NSCLC) by using exosomes derived from dendritic cells (DCs). Exosomes, small vesicles carrying molecular signals, can be loaded with antigens to boost the immune system's ability to fight cancer.

In clinical studies, patients with advanced NSCLC treated with antigen-loaded DC-derived exosomes showed promising results. These exosomes effectively stimulated the immune system, leading to improved outcomes, including longer survival times and better disease control, even with residual tumors.

Ensuring the safety of exosome-based therapies is crucial. Comprehensive pre-clinical studies are needed to evaluate potential side effects and toxicities. Proper characterization of exosomes, including detailed physicochemical data and immune-stimulating activity, is essential. Only exosomes loaded with the necessary antigens and demonstrating desired activity should be used, as unmodified exosomes showed no significant activity.

Standardized protocols are necessary for regulatory compliance and clinical application, ensuring that exosomes meet safety and efficacy standards. With these measures in place, exosome-based therapies show great promise for improving the treatment of advanced NSCLC and potentially other cancers.

> ***Antigen-loaded DC-derived exosomes show promising efficacy by stimulating the immune system and improving outcomes in advanced NSCLC, while ensuring safety requires comprehensive pre-clinical studies and proper characterization.***

A significant finding was that the activation of natural killer (NK) cells, rather than cytotoxic T lymphocytes (CTLs), was a better indicator of clinical response. NK cells directly target and destroy cancer cells, and their activation by the exosomes resulted in better clinical outcomes.

Summarized by Nova Yuli Prasetyo Budi, MD, PhD

UPCOMING MEETING

JOIN US!

ACTO MEETING 2024

HANGZHOU

cellular therapy;
industry and policy,
immunotherapy,
stem cell and cellular therapy
industry and policy

ACTO MEETING 2025

SINGAPORE

"HALAL CERTIFICATION" FOR CELL AND GENE THERAPY (CGT) PRODUCTS IN THE FUTURE

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

The global Muslim population is nearing 2 billion, approximately a quarter of the world's total population, and is projected to reach 3 billion by 2030. Among them, 62% are distributed in the Asia-Pacific region, 20% in the Middle East and North Africa, and 15% in Sub-Saharan Africa. Countries like Indonesia, Pakistan, India, Bangladesh, Turkey, and Egypt have a Muslim population of over 900 million, accounting for more than half of the global Muslim population. In comparison, Europe and the Americas only have 2% of the total Muslim population. This 2 billion-strong Muslim population is propelling the Halal market with the demand for "Halal Certification".

Halal Certification Market

The rapid growth of the Muslim population has driven the thriving development of the global "Halal Certification" market. The term "Halal" originates from Arabic, meaning "permissible" or "lawful," signifying adherence to Islamic law for Muslims. Under the standards of "Halal Certification," products must comply with stringent regulations, including the exclusion of pork or its derivatives, blood or blood products, toxic or harmful substances, alcohol as a food additive or in the manufacturing process, and other ingredients prohibited by Islamic law. These strict criteria ensure the quality and safety of Halal products, offering Muslim consumers options that align with their religious beliefs.

Beyond Muslim consumers, an increasing number of non-Muslim consumers are also seeking out Halal-certified products, perceiving them to be purer and healthier. According to the latest report from the German data company Statista in 2024, the global Halal market is projected to reach nearly $3 trillion by 2025. This growth underscores the substantial potential of the Halal market, garnering interest not only from Muslim communities but also from consumers worldwide.

Do Muslim Cell and Gene Therapy (CGT) Products Need to Comply with "Halal Certification"?

In the future, will Muslim CGT products also be required to adhere to "Halal Certification"? According to Presidential Decree No. 6/2023 issued by the Indonesian government on January 19, 2023, all drugs, biological products, and medical devices entering, circulating, and being sold in Indonesia, including CGT products categorized as biologics, must obtain "Halal Certification." This mandate encompasses all aspects of the business process, from materials and manufacturing to storage and packaging. The primary objective of this regulation is to

The rapid growth of the Muslim population and increasing interest from non-Muslim consumers are driving the global Halal Certification market, projected to reach nearly $3 trillion by 2025, while mandatory Halal certification for cell and gene therapy products in countries like Indonesia, Malaysia, UAE, UK, and Australia is set to reshape the global competitive landscape.

ensure that products meet Halal standards and fulfill the requirements of Islamic law, catering to the demand and faith considerations of Muslim consumers for Halal products. Specific criteria for "Halal Certification" include verifying that product ingredients are sourced from Halal components and confirming that the manufacturing process aligns with Halal methods in accordance with Islamic law.

Beyond Indonesia, other countries are also emphasizing Halal certification for pharmaceutical and biological products. For example, the Malaysian government has established a Halal pharmaceutical working group to develop standards, guidelines, and provide certification. The Ministry of Industry and Advanced Technology (MoIAT, formerly ESMA) in the United Arab Emirates has implemented regulations to ensure that all pharmaceutical products imported or manufactured in the country meet Halal standards. The UK and Australia have likewise introduced pharmaceutical regulations related to Halal standards. While the U.S. Food and Drug Administration (FDA) permits the use of porcine-derived ingredients in drugs, manufacturers must include label declarations.

"Halal Certification" Has the Potential to Reshape the Global Competitive Landscape of CGT Products

The mandatory requirement for Halal certification is set to establish a new framework for the CGT process, exerting a significant influence on the future global market for CGT products within the 2 billion-strong Muslim population. This necessitates manufacturers to assess existing or in-progress products and all reagents utilized in the process to guarantee adherence to Halal standards. Apart from meeting FDA prerequisites for the Certificate of Analysis (COA) from clinical trials, they must also ensure alignment with Halal standards. The implementation of "Halal Certification" could potentially redefine the global competitive environment for CGT products.

Rita Yen-Hua Huang, PhD

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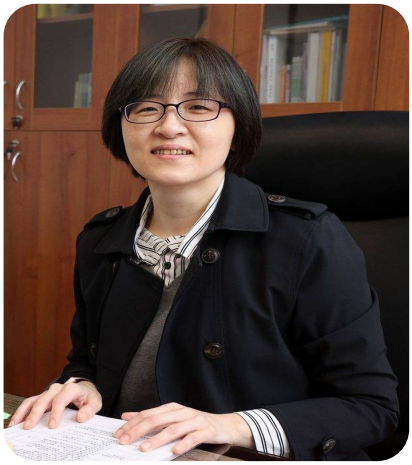
A NEW MILESTONE IN TAIWAN'S REGENERATIVE MEDICINE



LIU-YUEH PING

Director-general, department of medical affair

Ministry of health and welfare, taiwan

To meet the urgent needs of patients with unmet medical conditions, advanced countries are exploring innovative solutions like gene and cell therapy. Taiwan has responded admirably by passing the "regenerative medicine dual laws," marking a new milestone in its commitment to advancing regenerative medicine and supporting cutting-edge therapies.

To appropriately address the urgent needs of patients with "unmet medical needs" (such as terminal cancer patients or those with rare diseases), advanced countries are actively seeking solutions, focusing on medical innovations to increase the chances of saving lives. Gene and cell therapy are considered to be among the most promising emerging medical technologies. With advanced countries moving towards loosening and formulating new policies and regulations related to regenerative medicine, this trend has led companies to invest heavily in the cell and gene therapy industry. Concurrently, in line with the development of precision medicine and Industry 4.0, companies are integrating digital technologies such as artificial intelligence and big data analysis to promote the automated production processes of cell preparations, accelerating the global development of the cell and gene therapy industries.

Furthermore, there is an ongoing global initiative to establish comprehensive drug management systems that guarantee the safety, efficacy and quality of drugs through premarket review processes in order to safeguard public health. However, this well-intentioned and rigorous drug regulatory framework, after years of implementation, has led to the phenomenon of "marketing lag," raising concerns about patients' timely access to potentially effective drugs. In response to this need, the United States passed the world's first "Right to Try Act" in 2018, exempting unapproved drugs from regulatory review and allowing patients to use investigational drugs that have completed Phase I clinical trials based on physician assessment.

In the same year, Taiwan responded to the urgent demand for cancer immunotherapy from the public by passing amendments to the Regulation Governing the Application of Specific Medical Examination Technique and Medical Device (hereinafter referred to as the Specific Regulation), making it the second country after Japan to initiate a dual-track management system for regenerative medicine. The Specific Regulation mainly allows hospitals and cell processing units (CPUs) approved by the Ministry of Health and Welfare to collaborate and apply for the execution of six major low-risk autologous cell therapy projects. Since its implementation and after years of adjustments and revisions, the current stage includes indications for autologous immune cells, adipose stem cells and fibroblasts. As of the end of December 2023,

117 medical institutions and 50 cell therapy companies have submitted a total of 502 applications, with 258 cell therapy technologies approved (excluding terminated projects) and a total of 1,398 cases treated. With continuous international technological innovations, Taiwan's cell and gene therapy industry, supported by long-term development and regulatory policies, has advanced various cell therapy technologies and introduced intelligent automated production techniques through technical collaborations with domestic and international companies and institutions. This includes developing new cell/gene therapy technologies and products, such as γδ-T cells or bispecific antibodies and providing automated cell preparation CDMO services. These advantages give Taiwan a competitive edge in the field of cell and gene therapy and lay a solid foundation for future development.

Legislative Speaker Han Kuo-yu presided over the third and final reading of the Regenerative Medicine Act at the Legislative Yuan on Tuesday, June 4, Q. (CNA photo)

Given that cell and gene therapy is a global market, Taiwan faces the challenge of aligning with international standards and finding its place in the global market. To ensure Taiwan's cell and gene therapy management system aligns with major international countries, after years of collaborative efforts from all political parties, public and private groups and administrative departments, Taiwan passed the "regenerative medicine dual laws," which are the "Regenerative Medicine Law" and the "Regenerative Medicine Preparations Act," in June 2024, marking a new milestone in Taiwan's regenerative medicine. The "Regenerative Medicine Law" sets relevant management norms for entities performing regenerative medical techniques, such as businesses, hospitals and laboratories, to ensure the quality, safety, and efficacy of regenerative medical practices. Given the significant impact of regenerative medical practices on patients' lives, bodies or health, the law also imposes severe penalties, including fines of up to NT$20 million for non-medical institutions performing regenerative medical practices or advertising them and confiscating the equipment and regenerative preparations used by non-medical institutions for such practices. The "Regenerative Medicine Preparations Management Act" aims to allow patients with life-threatening or severely disabling conditions to use regenerative medical preparations early. It grants "temporary approval" for up to five years for regenerative medical preparations that have completed Phase II clinical trials and have demonstrated safety and preliminary efficacy through a risk-benefit assessment. The direction of Taiwan's regulations related to cell and gene therapy has been moving towards international regulatory norms, establishing relevant standards for companies to follow, ensuring that patients have access to treatment and laying the foundation for industrial development. Most importantly, through the "regenerative medicine dual laws," Taiwan hopes to perfect the ecosystem of the cell and gene therapy industry, promote the development of Taiwan's cell and gene therapy industry and enhance its international competitiveness.

THE DEVELOPMENT OF CELL THERAPY IN TAIWAN: FROM THE SPECIAL REGULATION ACT TO THE REGENERATIVE MEDICINE ACTS

Ming-Hao Teng[1], Yu-Xiu Lin[1], Thai-Yen Ling[1,2]

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[2]Director Board Member, Asian Cellular Therapy Organization (ACTO)

Taiwan has achieved significant milestones in the regulation of regenerative medicine. After nearly a decade of legislative efforts and multiple amendments, the Regenerative Medicine Act and the Regenerative Medicine Preparations Regulation were finally passed on June 4, 2024, and approved in the third reading by the Legislative Yuan.

Previously, the pressing health challenges faced by Taiwan have spurred the need for cell therapy, particularly for diseases that are inadequately managed by traditional treatments, such as cancer, degenerative diseases, and chronic conditions exacerbated by an aging population. The initiation of bone marrow transplants in the 1980s marked the beginning of cell therapy in Taiwan, representing the first case of cell therapy in the country.

The promotion of cell therapy in Taiwan has been primarily driven by academic research, government policy support, and international cooperation. Since the successful isolation of human embryonic stem cells in 1998, Taiwan has increased its investment and research in this field, aiming to carve out a significant presence in the global development of cell therapy. The establishment of the Taiwan Society for Stem Cell Research in 2005, in conjunction with the international ISSCR, further accelerated research and applications in this field, ushering in a new era of cell therapy in Taiwan. In 2013, Akihiro Shimosaka, the chairman of ACTO, was invited by Taiwan's National Health Research Institutes to host the fourth ACTO annual meeting, inviting participants from thirteen Asian countries as well as representatives from the US FDA and the European EMA. This event significantly raised awareness about the feasibility of cell therapy, leading to further explorations and regulatory developments in Taiwan.

In 2014, Taiwan established the "Regenerative Medicine Advisory Group" which began to formulate regulations for cell therapy, including standards for the application and review of clinical trials for human cell therapy products, laying the foundation for the management of cell therapy products in Taiwan and encouraging the development of domestic cell therapy research and products. However, until 2018, the regulatory framework was still incomplete.

Despite the absence of laws permitting the use of cell therapy, the demand from private patients was rising, and the industry was conducting clinical trials under existing review standards. Therefore, in September 2018, the Ministry of Health and Welfare's Medical Affairs Bureau passed the "Special Regulation on the Inspection, Testing, and Use of Medical Devices" (Special Regulation Act), opening up six types of cell therapy technologies that could be implemented in approved medical institutions in Taiwan. This act provided the first legal framework for cell therapy in Taiwan, aimed at regulating the application of cell therapy and protecting patient safety. As of June 30, 2024, the Ministry of Health and Welfare had received a total of 540 applications for cell therapy programs, of which 381 were approved, covering 1,607 cases (Table 1). However, this

law revealed issues such as insufficient regulation, inconsistent implementation standards, and a lack of transparency, limiting its effectiveness and credibility. Thus, Taiwan still needed to establish a more comprehensive legal framework for regenerative medical products.

To address the controversies and potential risks associated with the Special Regulation Act, after years of effort, Taiwan finally passed the "Regenerative Medicine Act" and the "Regenerative Medicine Preparations Regulation" in 2024, which were approved in the third reading by the Legislative Yuan. The Regenerative Medicine Acts strengthened clinical trial requirements, clearly regulated the sources and ethics of cells, and enhanced monitoring and review mechanisms to ensure safety and efficacy. These included stricter regulations on the use of allogeneic and xenogeneic cells to ensure the safety and scientific validity of treatments. Except for compassionate use, treatments would require clinical trials. The acts also prohibited the use of fetal cells and embryonic stem cells, and people with limited or no capacity to act needed notarized consent to provide cell sources, protecting vulnerable groups and strengthening ethical standards. Moreover, the regulations mandated annual public disclosure of treatment outcomes and medical quality information from medical institutions to safeguard public interests. With these standards and regulations, the implementation of cell therapy in Taiwan is more secure, marking a mature phase in Taiwan's legislation of regenerative medicine and establishing Taiwan as the third Asian country with specific laws regulating regenerative medicine.

Looking ahead, Taiwan's cell therapy sector will continue to focus on innovation and international cooperation. With the implementation of the Regenerative Medicine Acts, more domestic and international investments are expected, promoting innovation and growth in the local biotechnology industry. Furthermore, Taiwan will strengthen interdisciplinary collaboration, advancing personalized medicine and aiming to play a more significant role in the global field of cell therapy. These legislative revisions and innovative initiatives not only reflect Taiwan's commitment to public health but also contribute significantly to the advancement of global medical technology.

Category	Indication	Applications	Subtotal Applications	Approved Cases (under implementation)	Subtotal Approved Cases
Autologous CD34+ selection	Various	0	0	0	0
Autologous immune cell therapy	Hematological malignancies ineffective to standard treatment	10	329	7	252
	Stage 1-3 solid tumor ineffective to standard treatment	70		44	
	Advanced solid tumors	249		164	
Autologous adipose stem cell therapy	Severe limb ischemia & Chronic non-healing wounds	38	126	22	77
	Major burns & Skin trauma	1		0	
	Subcutaneous and soft tissue defects	24		8	
	Osteoarthritis & Articular cartilage defects	63		41	
Autologous fibroblast therapy	Skin defects: wrinkles, pits, scars	17	17	12	14
Autologous bone marrow-MSC therapy	Osteoarthritis & Articular cartilage defects	14	33	6	27
	Spinal Cord Injury	19		8	
Autologous chondrocyte therapy	Articular cartilage defects	12	12	10	11
Other non-scheduled cell therapy		23	23	0	0
Total			540	381	

Table 1. Summary of Cell Therapy Technology Applications and Approval Statistics in Taiwan (As of June 30, 2024)

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CAR-T

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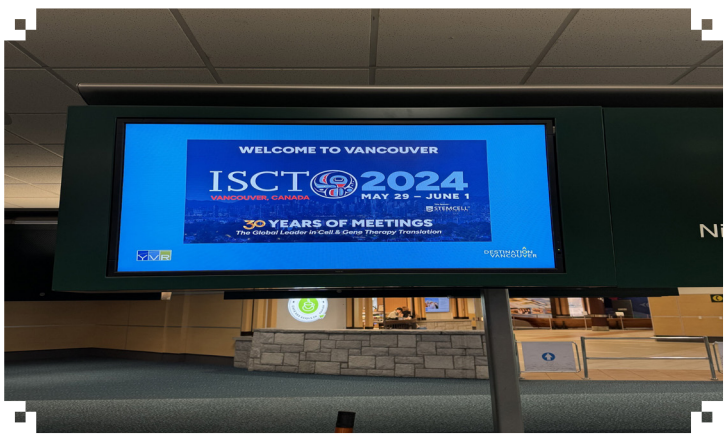
May 29 - Ju

“ISCT 2024 provided a un
the forefront of cell and g
in dynamic roundtable sessions
Translational Pathway Program,
and corporate sessions, staying at
The conference fostered deep d
and invaluable connections with
Those who joined ISCT 2024 we
advancements that are shaping the



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2024
LIGHT

une 1, 2024

EV

INDUSTRY

ique opportunity to engage with ene therapy. Participants engaged s, immersed themselves in the and attended global showcases t the cutting edge of the industry. iscussions, innovative solutions, experts and leaders worldwide. ere part of the conversations and future of cell and gene therapy.

VER, BC
ADA

MISEV 2023 GUIDELINE UPDATES

Summarized Josephine Diony Nanda, MD, PhD & Kajal, M.Sc.

The MISEV2023 guidelines, updated by the International Society for Extracellular Vesicles (ISEV), provide comprehensive recommendations for studying extracellular vesicles (EVs). These guidelines cover the latest methodologies for producing, separating, and characterizing EVs from various sources, including cell cultures, body fluids, and tissues. Key updates in MISEV2023 include new sections on EV release and uptake, as well as discussions on in vivo approaches to EV research. The guidelines emphasize addressing challenges such as EV nomenclature and distinguishing EVs from non-vesicular particles. Feedback from over 1,000 researchers helped shape these guidelines, ensuring they reflect current best practices and facilitate robust scientific discoveries in the EV field.

Extracellular vesicles (EVs), nano- to micro-sized particles released by all cell types, play crucial roles in a multitude of biological systems. Enclosed by a lipid bilayer membrane, EVs exhibit remarkable molecular and structural heterogeneity, which opens up vast potential for groundbreaking discoveries in both fundamental biology and therapeutic applications. However, this same complexity presents significant challenges throughout the stages of EV research, from isolation and characterization to functional analysis and clinical translation. Exploring the diverse functions and implications of EVs holds promise for advancing our understanding of cellular communication and developing innovative medical interventions.

To support the purpose of understanding EVs better while keeping the complexity in check, a guideline was proposed by the International Society for Extracellular Vesicles (ISEV), named Minimum Information for Studies of Extracellular Vesicles (MISEV). Following the 2014 and 2018 MISEV, the newest 2023 MISEV encompasses a wide range of topics, from nomenclature and technical details (collection and pre-processing, EV separation and concentration, EV characterization and its technique-specific), to further study including EV release and uptake, functional studies, and EV analysis in vivo.

This summary will deliver each topic and highlight the updates compared to the previous one.

A. Nomenclature

The updates on MISEV 2023 mainly focused on the updates of EV, NVEP, and NP definitions:

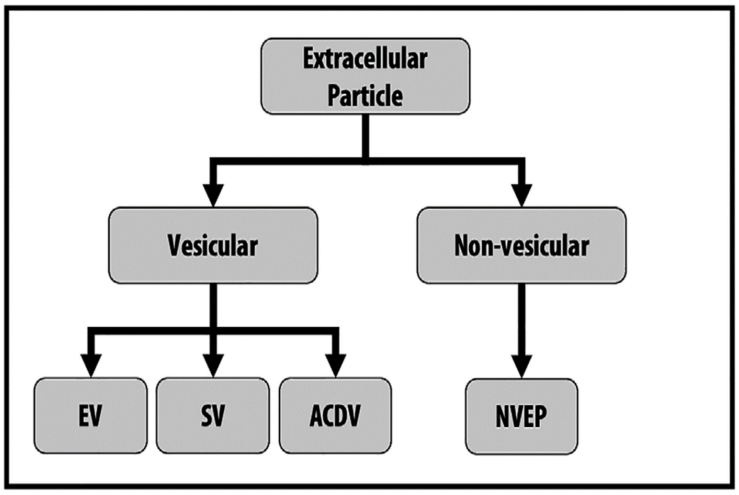
- Extracellular Vesicles (EVs): Defined as cell-released particles delimited by a lipid bilayer and unable to replicate on their own. Biogenesis terms are discouraged unless subcellular origin can be demonstrated for the specific EV source and condition.
- Non-Vesicular Extracellular Particles (NVEP): Accurate term for cell-derived multimolecular assemblies that are non-vesicular in nature.
- Extracellular Particles (NP): Overarching term for cell-derived multimolecular assemblies in the nanometer to micron size range, including both vesicular and non-vesicular entities.

EV Mimetics: EV-like particles produced through direct artificial manipulation. Artificial Cell-Derived Vesicles (ACDVs): EV mimetics produced in the laboratory under

conditions of induced cell disruption, such as extrusion.

- Synthetic Vesicles: EV mimetics synthesized de novo from molecular components or made as hybrid entities.
- Small and Large EVs: Based on the diameter of the separated particles measured using a specific characterization method; small EVs are often described as <200 nm in diameter, while large EVs are often described as >200 nm in diameter.

The usage of exosomes or ectosomes is limited to cases where a proven demonstration of subcellular origin is available. The usage of microvesicles and exosome-like vesicles is discouraged due to the ambiguity of their meeaning.



B. Collection and Pre-Processing

It is recommended to define the source of EVs, including its preparation and isolation, cell culture conditions (viability, passage number, and density), medium and additives used, types of culture, and environmental conditions of the culture (temperature, pH, gas concentrations, and physical stimuli). Cells from primary cultures should report harvesting methods and pre-culturing conditions.

Storage conditions pre- and post-EV-separation also influence EV yields, contents, functionality, and single particles to aggregates ratio. Sample pre-processing prior to separation is advisable to remove potentially interfering entities. Preservation at room temperature is stable for 6 hours to 2 months, depending on the source and EV condition, while -80°C is more appropriate for long-term storage. The effects of freeze-thaw cycles on EV properties are still conflicting, but the usage of cryoprotectants is proposed to reduce damage.

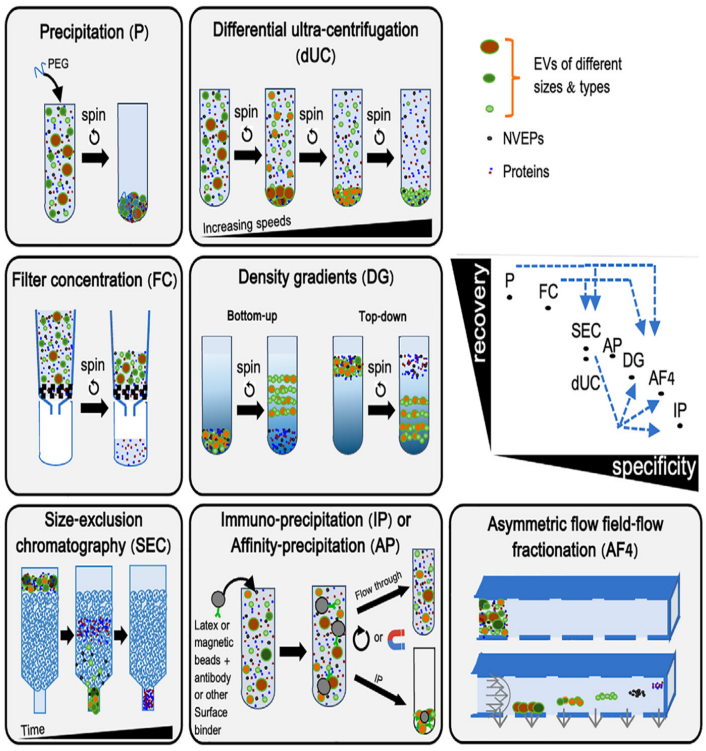
C. EV Separation and Concentration

Several EV separation and concentration procedures were tested for yield (recovery) and specificity. No methods currently produce both high yield and specificity simultaneously. Specificity can vary:

- Size Exclusion Chromatography (SEC): Separates EVs by size from many (but not all) NVEPs, but all EV types are recovered together.
- Differential Ultracentrifugation (dUC): Separates EV subtypes based on size/weight but co-isolates NVEPs at high speeds.
- Many 'exosome purification' kits use precipitation (P) or affinity precipitation (AP). Precipitation methods do not isolate pure exosomes or even EVs but a mixture of EPs, while affinity precipitation may be more specific to EVs but not exosomes.

Careful consideration is needed before deciding on the appropriate methods to serve the experiment's final purpose.

Figure 2. Some EV separation and concentration methods on a recovery (yield) versus specificity. Dashed blue arrows indicate combinations of methods resulting in increased specificity.



D. EV Characterization

To characterize EVs, several options could be used:

- Quantification of Particle Number Concentration: Often unreliable due to lack of specificity and sensitivity for EVs. Quantification of particle size should be presented with orthogonal measurements to increase size distribution confidence.

- Measurement of Total Protein: By colorimetric assays, fluorometric assays, global protein stain on SDS-PAGE, or absorbance readings. Protein concentration as a surrogate of EV concentration should be used with caution and is generally not recommended.

- Total Lipid Quantification: By colorimetric assays, fluorescence of membrane intercalating dyes, total reflection Fourier-transform infrared spectroscopy (FTIR), or chromatography. Total RNA Quantification: More sensitive

- methods preferred, such as Agilent Bioanalyzer pico chip or Quant-iT RiboGreen RNA Assay; for small RNAs, Qubit microRNA Assay kit.

- EV Morphology: Best assessed for smaller EVs using high-resolution imaging techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), cryo-EM, and scanning-probe microscopy (SPM), including atomic force microscopy (AFM).

MISEV 2023 recommends the five-component framework introduced in MISEV 2018 for reporting claims about the protein content of EVs. The presence of EV features is assessed in categories 1 and 2. Category 3 assesses purity from common contaminants. Categories 4 and 5 provide additional information on possible intracellular origins of EVs or co-isolates. At least one protein of categories 1, 2, and 3 should be analyzed as EV hallmarks to assess the presence of NVEPs in an EV preparation.

Non-protein markers of EVs, such as phosphatidylserine, glycans, or specific nucleic acids, are seldom EV-specific but in some cases may add support for the presence of a lipid bilayer or cytosolic components. Co-localization with protein markers may provide stronger evidence for the presence of EVs, especially for single-particle measurements. Non-protein markers may be detected directly by lipid mass spectrometry or Raman spectroscopy, or indirectly using fluorescent probes such as membrane labels or intraluminal dyes.

Table 1. Protein content-based EV characterization examples for proteins commonly found in mammalian cell-derived EVs.

		Cate
1- Transmembrane (or GPI-anchored) proteins associated with plasma membrane and/or endosomes All EVs Non-exhaustive examples, categorized a, b, c: by decreasing strength of membrane association.	**2- Cytosolic proteins in EVs** All EVs	**3-** All
1a: multi-pass transmembrane proteins. Tetraspanins (CD9, CD63, CD81, CD82); other multi-pass membrane proteins (CD47; heterotrimeric G proteins GNA*, TSAP6)	**2a: with lipid or membrane protein-binding ability.** ESCRT-I/II/III (TSG101, CHMP*) and accessory proteins: ALIX (PDCD6IP), VPS4A/B; ARRDC1; Flotillins (FLOT1/2); caveolins (CAV*); syntenin (SDCBP)	**3a:**
1b: single-pass transmembrane proteins. Major Histocompatibility Class I or II, Integrins (ITGA*/ITGB*), transferrin receptor (TFR2); LAMP1/2; heparan sulphate proteoglycans including syndecans (SDC*); EMMPRIN (BSG); ADAM10	**2b: promiscuous incorporation into EVs (and possibly NVEPs).** Heat shock proteins HSC70 (HSPA8), and HSP84 (HSP90AB1) note that both are abundant also in NVEPs; cytoskeleton: actin (ACT*), tubulin (TUB*); enzymes (GAPDH)	**3b:** YW
1c: GPI- or lipid-anchored proteins. Glypicans (GPC1), 5′nucleotidase CD73 (NT5E), complement-binding protein CD59		**3c:**

E. Technique-Specific for EV Characterization

Relevant reporting criteria have increased to ensure reliable and reproducible data interpretation. The techniques listed are commercially available and supported by existing literature:

Flow cytometry-based methods: Single-EV flow cytometry, Bead-based flow cytometry Genetic protein tagging Mass spectrometry proteomics Microscopy-based methods: Atomic force microscopy, Diffraction-limited fluorescence microscopy,

Dynamic light scattering, Electron microscopy, Nanoparticle tracking analysis, Single-particle interferometric reflectance imaging sensing, Super-resolution microscopy Nucleic acid characterization Protein- and non-protein labeling of EVs Raman spectroscopy Resistive pulse sensing Western blotting

gory		
Major components of non-EV co-isolated structures (NVEPs) EVs as purity control	**4- Transmembrane, lipid-bound and soluble proteins associated with intracellular compartments other than PM/endosomes** Subtypes of EVs and/or pathologic/atypical state, and/or novel separation method	**5- Secreted proteins recovered with EVs** Corona or functional component of EVs
lipoproteins. Produced mostly by liver, abundant in plasma, serum. Apolipoproteins	**4a: nucleus.** Histones (HIST1H**); Lamin A/C (LMNA/C)	**5a: blood-derived corona proteins.** Partially overlapping with 3a/3b: apolipoproteins, complement, fibrinogen
protein and protein/nucleic acid aggregates. Immunoglobulins (blood); Tamm-Horsfall protein (Uromodulin/UMOD; urine); albumin. YWHA* (14-3-3*) and AGO* (can be present in EVs but generally more abundant in NVEPs).	**4b: mitochondria.** VDAC, cytochrome C (CYC1); TOMM20	**5b: cytokines and growth factors.** e.g., TGFB1/2; IFNG, VEGFA, FGF1/2, PDGF*, EGF, interleukins (IL*)
exomere or supermere-enriched components. HSP90AA/B, TGFBI, HSPA13, LDHA/B	**4c: secretory pathway.** Endoplasmic reticulum, Golgi apparatus: calnexin (CANX); Grp94 (HSP90B1); BIP (HSPA5), GM130 (GOLGA2)	**5c: adhesion and extracellular matrix proteins.** Fibronectin (FN1), Collagens (COL**), MFGE8; galectin3-binding protein (LGALS3BP), CD5L; fetuin-A (AHSG)
	4d: others. Autophagosomes, cytoskeleton… LC3 (MAP1LC3A), Actinin1/4 (ACTN1/4)	

F. EV Release and Uptake

EV release can be visualized using various methods, including those employing fluorescent tags and dyes. MISEV 2018 addressed the inhibition of EV release through genetic manipulations and drugs, such as RAB27A/B knockdown and ARRDC1 inhibition. When reporting genetic and pharmacological manipulations used to inhibit or stimulate EV secretion, it is important to consider their potential effects on other secretory or cellular processes.

EVs interact with target cells through binding, internalization, and fusion/content delivery. Most reports of EV function assume content delivery, but uptake may be low in some target cells, requiring a high ratio of EVs to target cells for visualization. By labeling specific EV subtypes, blocking their biogenesis, and assaying cargo delivery, researchers can explore how EV-target cell interaction mechanisms vary between different EV subtypes and donor-acceptor combinations.

G. Functional Studies
MISEV 2018 recommendations on functional studies of EVs continue to hold for MISEV 2023:

Physiologically informed dose-response and time-course studies are encouraged. Carefully selected EV negative controls are needed to assess the contribution of 'background' EV activity. Controls consisting of non-EV-containing, EV-depleted, or enzymatically treated EV separation fractions can help identify if a function is specific to EVs or associated with co-isolating materials.

H. EV Analysis In Vivo

In vivo EV studies offer valuable insights into EV release, biodistribution, pharmacokinetics, and function. These studies typically involve introducing exogenous EVs into an organism, which may be unlabeled if targeting a disease or physiological outcome without imaging. For imaging studies, EVs are often labeled with fluorescent or bioluminescent markers.

Detecting and tracking both endogenous and exogenous EVs require careful consideration of technical limitations such as technique-specific sensitivity and spatial resolution. It is crucial to account for the potential impact of EV labeling on their biodistribution, pharmacokinetics, and function. Additionally, pharmacologic or genetic manipulations aimed at inhibiting EV production in vivo may have unintended off-target effects, and the behavior of endogenous and exogenous EVs might differ.

In conclusion, MISEV 2023 has compiled comprehensive recommendations for EV research, covering both fundamental and advanced technologies and methodologies. This document serves as a valuable resource for newcomers to the field and as a source of inspiration for more advanced research. The creation of these guidelines involved achieving a high level of consensus among a broad group of scientists within the EV community. While acknowledging that the field is dynamic and new methods will continue to emerge, MISEV 2023 represents the current best practices and consensus within the extracellular vesicle research community.

2024 ISCT VANCOUVER OBSERVATION NOTE

Yi-Pei Hung

UnicoCell CO., LTD., June 2024

ISCT offers various programs supporting the scientific, regulatory, and commercialization pillars of the society, providing networking and partnership opportunities for over 500 delegates. The society also offers a full-week training course to meet the needs of the CGT field.

ISCT 2024 Vancouver was a complete success, marking the 30th anniversary of the International Society for Cell & Gene Therapy (ISCT). Exclusive loyalty pins were awarded to delegates who had accumulated multiple meeting attendances. This was the largest ISCT meeting to date, with 2,777 delegates and over 600 abstract presenters from 61 countries. The conference featured extensive global networking and included a voluntary 5K run on the third day of the four-day event.

The conference highlighted various fields in cell and gene research, including Immunotherapy (CAR-Ts, T Reg, NK Cells, etc.), iPSCs and iPSC-derived cells, Exosomes/Extracellular Vesicles, Mesenchymal Stem/Stromal Cells, Hematopoietic Stem/Progenitor Cells and Engineering, Gene Editing/Gene Therapies, and Tissue Engineering. These topics were explored through roundtable sessions, concurrent sessions, corporate sessions, elevator pitch presentations, and pitch sessions.

On the first day, about 50 roundtable discussions addressed key CGT (cell and gene therapy) issues, including eight main topics: Clinical & Therapeutic Development, Basic and Discovery Research, Bioprocessing & Manufacturing, Workforce Development, Global CGT Markets, Regulation & Policy, COGs & Business Models, and Tools & Tech.

The roundtable sessions were workshop-like, leveraging expertise to tackle practical problems in cell and gene therapy, fostering collaboration for practical solutions. These discussions were particularly inspiring for attendees. For example, the session on Understanding the Fundamentals of MSC Biology discussed MSCs' interactions with various cell types and highlighted the importance of MSC potency. Researchers shared experiences from clinical trials, noting that while efficacy, clinical outcomes, and safety are less of a concern, the mechanism of action and potency are emerging as crucial focuses. This session was related to another roundtable, Back to the Future: Setting Up MSCs Clinical Trials for Success, where pioneers whose MSC products have been approved shared their views on MSC characterization and potency assays. This discussion echoed issues raised at the APACRM meeting in Japan regarding the necessity of potency, blinding design, and dose dependence in cell therapy trials, further debated in the Regulation & Policy session on Demonstrating Comparability: Are Potency Assays Necessary?

This year, interesting topics highlighted the real-world benefits and challenges of CGT, including:

Japan's 10-year experience in regulating clinical access for unapproved and unproven cell therapies: Emerging Shadow Markets in CGT, Can You Protect Your Patients From Unproven Therapies: A model for other markets? Preparing for AI: Anticipating Regulatory Challenges. Emerging Shadow Markets in CGT, Can You Protect Your Patients From Unproven Therapies? The Post-Marketing Authorization, Elephant in the Room: Who Pays the Bill? The debate over using fresh or post-thaw cells was particularly heated during the Beyond the Dead (MSCs) session. Representatives from Mayo Clinic shared their successful model for industry collaborations and innovative projects in another session.

On the final day, two signature series on iPSCs and Exosomes addressed regulatory approval challenges from bench to bedside. Discussions highlighted varied views on the benefits of Secretome, EV, or Exosome, emphasizing the importance of robust production processes and standardized methodologies. ISCT offers various programs supporting the scientific, regulatory, and commercialization pillars of the society, providing networking and partnership opportunities for over 500 delegates. The society also offers a full-week training course to meet the needs of the CGT field.

A highlight of the meeting was the appearance of Emily Whitehead and her father, Tom Whitehead, who shared their inspiring story of battling ALL, deeply touching and motivating the audience. Indeed, scientific exploration is crucial to CGT development, with regulatory parties playing a vital role in protecting patients' rights. The ISCT Global Regulatory Perspectives (GRP) workshop, held annually alongside the Society's Annual Meeting, underscores the collaboration between international regulatory bodies, industry, clinicians, and academia, highlighting the crucial role of regulatory parties in CGT development and patient rights.

THE JOURNEY OF HOPE: RESETTING AUTOIMMUNITY

In the world of medical research, there's a continuous quest to find innovative treatments for debilitating conditions. One such realm of focus has been autoimmune diseases—chronic illnesses where the immune system mistakenly attacks the body. Diseases like systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, and systemic sclerosis present significant challenges, often requiring long-term suppression of the immune system to manage symptoms. Imagine a world where this persistent suppression is no longer necessary, where the immune system could be reset to eliminate the underlying cause of these diseases. This story follows a groundbreaking approach to achieving such a goal through the deep depletion of B cells using chimeric antigen receptor (CAR) T-cell therapy.

A New Dawn in Treatment

In an ambitious study, a group of 15 patients—each grappling with severe autoimmune diseases—embarked on a novel treatment journey. Eight of these individuals suffered from SLE, three from idiopathic inflammatory myositis, and four from systemic sclerosis. They had all endured relentless disease progression and had shown resistance to at least two standard treatments. Their hope lay in a single infusion of CD19 CAR T cells, following a preconditioning regimen with fludarabine and cyclophosphamide.

The Method

The patients received their personalized CAR T cells, which had been engineered to target and deplete B cells expressing the CD19 protein. This procedure was meticulously planned and executed, involving advanced technology to ensure the consistency and potency of the CAR T cells. The treatment was offered through an expanded-access program in Germany, ensuring that all patients gave their informed consent.

Tracking Progress

Over the next two years, the efficacy of the CAR T-cell therapy was evaluated using several clinical criteria. For SLE, the Definition of Remission in SLE (DORIS) remission criteria was employed. For idiopathic inflammatory myositis, the American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) major clinical response was measured. Systemic sclerosis was assessed using the European Scleroderma Trials and Research Group (EUSTAR) activity index. Safety was also closely monitored, including the occurrence of cytokine release syndrome and infections.

Promising Results

As the months rolled on, the results were nothing short of remarkable. The median follow-up time was 15 months, with some patients monitored for as long as 29 months. The duration of B-cell aplasia (a state where B cells are absent) was an average of 112 days. Every patient with SLE achieved DORIS remission, those with idiopathic inflammatory myositis reached major clinical response, and the systemic sclerosis patients saw a decrease in their disease activity scores.

The implications were profound: immunosuppressive therapy was completely stopped in all patients. There were some manageable side effects, including mild cytokine release syndrome in most patients, and more severe cases in a few, which were successfully treated. There were no cases of severe neurotoxicity, and only one patient was hospitalized due to

pneumonia.

A Step Towards a Cure

This case series showcased the feasibility, safety, and potential of CD19 CAR T-cell therapy in treating severe autoimmune diseases. The ability of this therapy to induce sustained drug-free remission was a beacon of hope, signaling a significant leap forward in autoimmune disease treatment.

The Science Behind the Story

CAR T-cell therapy has already revolutionized the treatment of certain cancers, particularly hematologic malignancies. By targeting malignant B cells, it has significantly improved outcomes. This study explored its potential in autoimmune diseases, where autoreactive B cells cause similar havoc. Traditional treatments have focused on using antibodies to deplete or inhibit these cells, but achieving long-term remission remained elusive. CAR T-cell therapy offered a new hope by targeting CD19, a protein widely expressed on B cells and plasmablasts.

The Path Forward

Although these initial results were promising, they marked the beginning of a longer journey. Controlled clinical trials are needed to confirm the findings and refine the treatment. The story of these 15 patients serves as a powerful testament to the potential of CAR T-cell therapy, offering a glimpse into a future where autoimmune diseases might be managed more effectively, and perhaps even cured.

This narrative of innovation and perseverance in the face of chronic illness highlights the relentless quest of researchers and clinicians to bring new hope to patients around the world. The journey continues, with each step bringing us closer to transforming the lives of those affected by autoimmune diseases.

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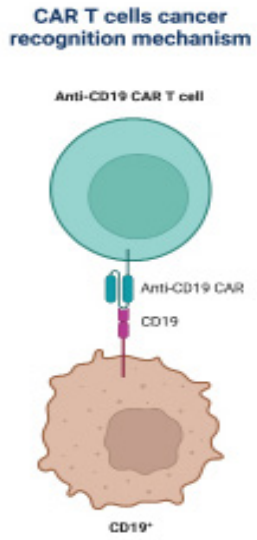

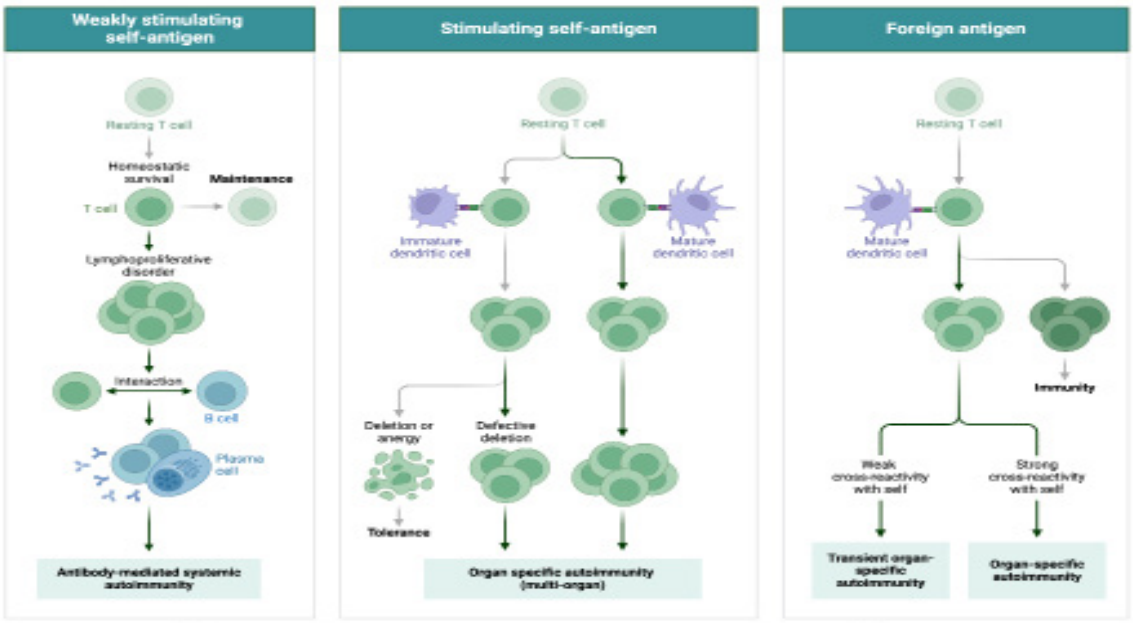

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CAR-T CD19 FOR AUTOIMMUNE DISEASE SLE

A New Frontier in Autoimmune Disease Treatment: CD19-Targeted CAR T-Cell Therapy for SLE In the intricate world of autoimmune diseases, B cell depletion has emerged as a potent strategy for treatment. This approach has shown remarkable success in conditions like rheumatoid arthritis (RA). However, systemic lupus erythematosus (SLE), a more complex autoimmune disorder, has proven more challenging. Despite initial promise, the B cell depleting anti-CD20 antibody rituximab failed to meet clinical endpoints in two large phase III trials almost a decade ago. Today, hope is rekindled with a novel approach: CD19-targeted chimeric antigen receptor (CAR) T cell therapy.

The Promise of CAR-T Cells

"The methodology involves inserting an artificial gene into the chromosomes of the patients' own T cells," explains Marko Radic, the corresponding author of a new study published in Science Translational Medicine. "The new gene encodes a CAR that targets CD19 on the majority of B cells and kills them upon binding."

This approach deviates from standard CAR T cell methods by using purified CD8+ T cells, thereby avoiding potential disease-promoting effects from CD4+ T cells. The second-generation CAR used in this study features a modified CD3ζ C terminus, designed to dampen its activity and prevent T cell exhaustion, thus increasing the persistence of the therapy.

Unlike rituximab, which requires repeated administration to maintain therapeutic doses, CAR T cell therapy could potentially lead to long-lasting remission. Previous trials of rituximab showed variable degrees of B cell depletion, with the most improvement seen in patients who experienced rapid, large, or long-lasting depletion. Incomplete or transient depletion of tissue-resident B cells might have contributed to rituximab's lack of efficacy in SLE trials.

"Compared with rituximab, the new approach has two main advantages," remarks Ignacio Sanz, an expert in anti-B cell therapies for SLE who was not involved in the study. "Firstly, anti-CD19 targeting eliminates a larger fraction of B cells, including pre-B cells, as well as a significant fraction of antibody-producing plasmablasts and plasma cells. Secondly, anti-CD19 CAR T cells can induce deeper and longer-lasting B cell depletion, as reported in lymphoid malignancies."

The Breakthrough in Animal Models Radic and colleagues tested this innovative therapy in two mouse models of SLE: NZB/W and MRL-lpr mice. The results were striking. The treatment achieved complete and sustained CD19+ B cell depletion, accompanied by a reduction in autoantibody production. Treated mice showed considerable improvements in various disease measures, including kidney function, spleen size, lymphocyte subset ratios, and skin inflammation. Remarkably, the treated mice attained a nearly normal lifespan.

Although CD19 expression was effectively diminished in the kidneys, spleen, and bone marrow, immunoglobulin light chain expression persisted in the spleen and bone marrow. This indicated the continued presence of some B cells at these sites, possibly explaining the preserved levels of IgM and IgG antibodies in the serum.

Further evidence of the therapy's persistence was demonstrated when adoptively transferred B cells were effectively depleted in mice that had received CAR T cell therapy months earlier. Additionally, adoptive transfer of T cells from treated mice to untreated recipient mice induced B cell depletion and reduced disease activity, indicating that the effects of this therapy are cell-mediated.

A New Horizon for Autoimmune Disease Treatment "Progress with CAR T cells in cancer over the past few years and the FDA approval of this therapy in 2018 indicate that the use of CAR T cell therapy is maturing and reaching a level of safety and acceptability in the clinic that might make it attractive to rheumatologists," concludes Radic.

Ignacio Sanz adds, "This work provides a strong rationale for the use of CAR T cells for the treatment of human autoimmune diseases and, in particular, for SLE. The natural next step in the field is the design of human clinical trials to assess the safety and efficacy of this approach in SLE and other autoimmune diseases, including ANCA-associated vasculitis, where repeated rituximab treatments might be necessary to sustain disease remission."

With the advent of CD19-targeted CAR T-cell therapy, a new chapter begins in the fight against autoimmune diseases. As researchers move forward, there is renewed hope for patients who have long struggled with conditions like SLE, offering a potential path to long-lasting remission and improved quality of life.

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CAR-T CD19 FOR MYASTHENIA GRAVIS

A Tale of Hope: CD19 CAR T-Cel

Therapy for Refractory Myasthenia Gravis In the vast landscape of medical research, a groundbreaking study published in The Lancet Neurology opened new doors for treating myasthenia gravis, a debilitating autoimmune disorder. The study demonstrated the feasibility of using transiently expressed B-cell maturation antigen (BCMA)-targeted RNA chimeric antigen receptor (CAR) T-cell therapy. Inspired by these findings, a team of dedicated scientists embarked on a journey to explore a different approach, targeting CD19 with a stably expressed CAR following a conventional lymphodepleting regimen. Their mission was to find a safe and effective treatment for severe and refractory myasthenia gravis.

The Patient's Journey

Our story centers on a 33-year-old woman who had been battling anti-AchR-positive generalized myasthenia gravis since 2012. Over the years, she endured significant challenges, including difficulties swallowing and breathing, and became unable to walk without assistive devices. From November 2021 to May 2023, her condition worsened, leading to several myasthenic crises and five admissions to the intensive care unit for invasive ventilation.

Despite numerous treatment attempts, including thymectomy, acetylcholinesterase inhibitors, B-cell-depleting antibodies (rituximab), proteasome inhibitors (bortezomib), immunosuppressive drugs (mycophenolate mofetil), and immunoglobulin therapy, her disease remained refractory. By March 2023, despite being on a combination of glucocorticoids, mycophenolate mofetil, and bortezomib, her clinical progression continued unabated.

A Ray of Hope

Given the refractory nature of her condition, the team decided to employ a novel CAR T-cell approach, leveraging the success of anti-CD19 CAR T cells in treating autoimmune rheumatic diseases. They opted for a CAR construct designed to produce lower cytokine levels and reduced toxicity. The patient underwent leukapheresis and CAR T-cell infusion after tapering ongoing immunosuppression to low-dose glucocorticoids. The researchers used a second-generation anti-CD19 CAR T construct (KYV-101) with a fully human CD19 binding domain.

Following successful in vitro expansion and lymphodepletion with fludarabine and cyclophosphamide, the patient received a single infusion of anti-CD19 CAR T cells. The results were nothing short of miraculous. By day 8, circulating CD19 B cells were eliminated, and by day 62, they had not reconstituted. There was a remarkable 70% reduction in pathogenic anti-AchR antibodies, while protective vaccination IgG titres were maintained.

A Miraculous Recovery

The patient's clinical improvement was evident within the first two months after the CD19 CAR T infusion. She experienced a significant increase in muscle strength and reduced fatigue. She could hold her arm out horizontally for longer periods and walk without supportive devices. The clinical multiparameter Besinger disease activity and Quantitative Myasthenia Gravis scores showed a marked improvement.

Despite the treatment, the patient had no adverse events such as cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or insufficient haematopoietic reconstitution. Only a self-limiting grade 1 transaminitis occurred, which resolved without treatment.

The Promise of a New Dawn This remarkable case, combined with previous observations in patients with autoimmune rheumatic diseases, suggests that anti-CD19 CAR T-cell therapy holds promise for a broad range of diseases driven by autoreactive B cells and autoantibodies. As researchers continue to explore and refine this groundbreaking approach, the future looks brighter for those who have long suffered from the relentless grip of autoimmune diseases.

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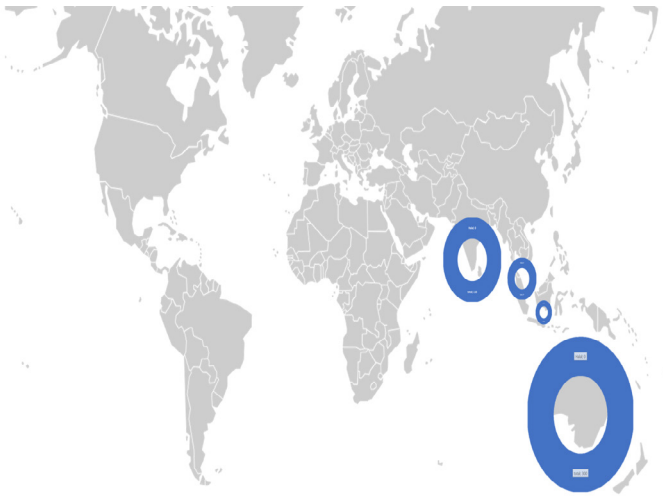
Summarized by Nova YP Budi, MD, PhD

GLOBAL PERSPECTIVE ON CGT HALAL CERTIFICATION



Summarized Nova Yuli Prasetyo Budi, MD, PhD

In the past decade, there has been a notable rise in both stem cell research and their clinical applications in Indonesia. This surge encompasses a broad spectrum of studies and clinical trials, highlighting the region's growing commitment to advancing regenerative medicine. Researchers have been increasingly exploring the therapeutic potential of stem cells, leading to more frequent and diverse clinical implementations aimed at treating various medical conditions. Given that the majority of Indonesia's population is Muslim, halal certification for stem cell and gene therapy products is crucial.

Halal certification is essential for ensuring that products conform to Islamic dietary laws and ethical standards. In the context of cell and gene therapy, this certification guarantees that these advanced medical treatments comply with Islamic principles, offering assurance to Muslim consumers.

Halal compliance in medicine involves ensuring that substances such as cells, tissues, and genetic materials, along with the processes of handling and administration, meet Islamic dietary and ethical laws. Islamic law emphasizes ethical treatment and prohibits the use of haram (forbidden) substances unless in cases of necessity where no halal alternatives are available.

Importantly, halal certification for CGT products is particularly significant in regions with large Muslim populations. Regions like Indonesia, Pakistan, India, Bangladesh, and Malaysia have substantial Muslim demographics, making adherence to halal standards a critical aspect of medical treatment acceptance and usage. It not only aligns medical products with religious and ethical standards but also fosters trust and acceptance among Muslim patients, ultimately contributing to better health outcomes and market growth for these advanced therapies.

Biological products requiring certification include enzymes, monoclonal antibodies, hormones, stem cells, gene therapies, vaccines, blood products, recombinant DNA products, and immunosera. Medical devices must also be certified if they contain animal-derived materials.

Key aspects of halal certification:

- Products must be made from halal materials and follow halal manufacturing processes.
- The halal process encompasses raw material sourcing, production, storage, and packaging.
- Materials must not be derived from prohibited sources, must not come into contact with non-halal materials, and must originate from animals slaughtered according to Islamic law if they are animal-derived.
- Companies must document and demonstrate their commitment to halal practices.
- Facilities used for halal production must be separate or thoroughly cleaned if shared with non-halal production.
- Continuous monitoring and internal audits are required to maintain certification.

Cell and Gene Therapy (CGT) products must comply with these halal standards in sourcing, production, and handling to be marketed in Indonesia. This comprehensive adherence to Islamic principles ensures the entire production chain is halal, providing Muslim consumers with the confidence that their medical treatments align with their religious beliefs.

Challenge of Halal CGT certification

While many clinical trials are already underway, significant challenges in achieving halal certification for CGT persist. These challenges include the complexity of ingredients and processes, regulatory differences, integration of scientific and religious knowledge, traceability and documentation, cost implications, rapid technological advancements, ethical considerations, and building consumer trust. Addressing these issues requires coordinated efforts to ensure that CGT products meet halal standards while advancing medical innovation.

1. Complexity of Ingredients and Processes:

Sources of Biological Materials: CGT often involves using cells, tissues, and genetic materials that may be derived from various sources, including animals, which must be halal. Ensuring that these materials comply with halal standards is challenging, especially when the origins are complex or undocumented.

Biological Manufacturing Processes: The production processes for CGT products are intricate and may involve various stages that need to be individually certified as halal. Ensuring every step, from cell culture to gene editing, adheres to halal guidelines is labor-intensive and requires rigorous oversight.

2. Regulatory Differences:

Varied Standards: Different regions with significant Muslim populations might have varying standards and interpretations of what constitutes halal, leading to discrepancies in certification requirements. Aligning CGT products with multiple standards can be challenging for manufacturers.

Evolving Regulations: As CGT is a rapidly advancing field, regulations and guidelines related to halal certification may frequently change, necessitating continuous updates and adjustments by companies.

3. Scientific and Religious Knowledge Integration:

Interdisciplinary Expertise: Effective halal certification requires a deep understanding of both the scientific aspects of CGT and the religious principles of halal. This necessitates collaboration between scientists, medical experts, and religious scholars, which can be difficult to coordinate.

Education and Awareness: There may be a lack of understanding among researchers and manufacturers about the specific requirements for halal certification. Education and training programs are needed to bridge this knowledge gap.

4. Traceability and Documentation:

Comprehensive Traceability: Ensuring the traceability of all ingredients and materials used in CGT to guarantee they are halal-certified is challenging. This involves meticulous record-keeping and supply chain management.

Documentation Requirements: Companies must maintain extensive documentation to demonstrate compliance with halal standards, which can be burdensome and resource-intensive.

5. Cost and Resource Allocation:

Financial Implications: The process of obtaining halal certification can be costly, involving fees for certification bodies, potential alterations to production processes, and ongoing compliance costs.

Resource Allocation: Smaller companies or startups in the CGT field may struggle with the additional resources needed to meet halal certification requirements.

6. Innovation and Ethical Considerations:

Rapid Technological Advancements: As CGT technologies evolve rapidly, keeping halal certification guidelines up-to-date with new scientific developments is a continuous challenge.

Ethical Dilemmas: Certain CGT approaches may raise ethical questions within the context of Islamic principles, necessitating nuanced discussions and rulings by religious authorities.

7. Market and Consumer Trust:

Consumer Skepticism: Despite certification, there may be skepticism among Muslim consumers about the compliance of CGT products with halal standards. Building and maintaining trust requires transparent communication and education.

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ADVANCEMENTS IN HUMAN STEM CELL RESEARCH IN INDONESIA: CLINICAL APPLICATIONS AND ETHICAL ISSUES

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In recent years, stem cell research in Indonesia shows remarkable progress over the past few decades. As global interest in regenerative medicine grew, Indonesia began to recognize the potential of stem cell therapy to address various health challenges. This led to increased government support, funding, and the establishment of specialized research institutes. The country's commitment to stem cell research highlights its dedication to addressing health challenges and improving the quality of life for its population, to make Indonesia as a competitive and forward-thinking player globally. In this review, we highlighted the overview of stem cell research in Indonesia, current advancements of cell therapy in Indonesia, clinical applications of stem cells, regulatory framework in Indonesia, and challenges and future directions. In conclusion, due to ethical issues, key advancements in stem cell research and therapy focus on the use of adult stem cells for various conditions. Stem cell applications has been done in orthopedic cases, cardiovascular diseases, hematologic diseases, burns and skin rejuvenation, neurologic conditions, infectious diseases, diabetes, and COVID-19, which were conducted as research based cell therapy services. Future prospects for stem cell research in Indonesia are challenging as it is crucial to ensure the safety and efficacy of the treatments. To address these challenges collaborative efforts among academia, government, business, as well as community and media are required.

Introduction

In recent years, stem cell research in Indonesia has seen remarkable progress over the past few decades. Stem cell therapy has emerged as an up-and-coming and advanced area of scientific research, generating significant expectations for new treatment methods.1 Initially, the focus was primarily on understanding the basic science of stem cells and their potential applications. Early efforts were driven by a small number of dedicated scientists and research institutions, laying the groundwork for more comprehensive studies. As global interest in regenerative medicine grew, Indonesia began to recognize the potential of stem cell therapy to address various health challenges. This led to increased government support, funding, and the establishment of specialized research institutes. Collaborative efforts between Indonesian researchers and international experts have further propelled the field, resulting in significant advancements and a growing body of knowledge.2 Today, stem cell research in Indonesia is poised to contribute to innovative treatments and improved healthcare outcomes for the population.

Stem cell research holds significant potential for advancing medical science and improving healthcare outcomes in Indonesia. As the country grapples with a range of health challenges, including chronic diseases, degenerative conditions, and injuries, stem cell therapy offers promising solutions, especially considering that almost 10% of respondents in Indonesia have non-communicable diseases (NCDs).3 This cutting-edge research paves the way for innovative treatments that can regenerate damaged tissues and organs, offering new hope for patients with conditions that were previously deemed untreatable. Furthermore, the development of stem cell-based therapies can reduce the reliance on traditional treatments and surgeries, leading to less invasive and more effective healthcare options.4 By

investing in stem cell research, Indonesia can enhance its medical capabilities, foster scientific innovation, and ultimately improve the quality of life for its population. This research aligns with the nation's goals of advancing public health and achieving sustainable medical progress. The country's commitment to stem cell research highlights its dedication to addressing health challenges and improving the quality of life for its population, positioning Indonesia as a competitive and forward-thinking player on the global stage. In this review, we highlighted the overview of stem cell research in Indonesia, current advancements of cell therapy in Indonesia, clinical applications of stem cells, regulatory framework in Indonesia, and challenges and future directions.

Overview of Stem Cell Research in Indonesia

Stem cells are unique cells with the ability to develop into different cell types and self-renew, making them crucial for growth, development, and tissue repair.1,5 There are three main types of stem cells, such as embryonic stem cells, adult stem cells and induced pluripotent stem cells (iPSCs). Embryonic stem cells (ESCs) are derived from early-stage embryos, specifically from the blastocyst. These cells possess pluripotency, meaning they have the ability to differentiate into nearly any cell type in the body6. This remarkable versatility holds significant potential for regenerative medicine and research. Unfortunately, in Indonesia, the use of embryonic stem cells is illegal due to ethical and religious concerns.7 The process of deriving ESCs involves the destruction of embryos, which raises significant moral and ethical issues, particularly in a country where the majority of the population adheres to religious beliefs that value the sanctity of early human life. These ethical considerations have led to stringent regulations and a ban on ESC research, directing scientific efforts towards alternative types of stem cells, such as adult stem cells and induced pluripotent stem cells (iPSCs), which do not involve the same ethical dilemmas.

Adult stem cells, found in various tissues like bone marrow, brain, and muscle, are integral for tissue maintenance and repair. They are typically multipotent, meaning they can differentiate into a limited range of related cell types.8,9 Research and therapies involving adult stem cells are actively pursued in Indonesia, as they do not involve the ethical issues associated with embryonic stem cells. Meanwhile, induced pluripotent stem cells (iPSCs), on the other hand, are created by reprogramming adult cells to revert to a pluripotent state, similar to embryonic stem cells. This innovation allows scientists to generate versatile stem cells from a patient's own tissues, minimizing the risk of immune rejection and sidestepping the ethical controversies. 10 In Indonesia, iPSCs are being explored for their potential in personalized medicine, disease modelling, and regenerative therapies.11–13 The focus on adult stem cells and iPSCs enables Indonesia to advance its stem cell research within an ethical framework, promoting scientific progress and improved healthcare outcomes.

The analysis of Indonesia's publications on stem cells has revealed a rapid increase in quantity year-by-year from 2003. In 2018, Indonesia's research landscape saw significant development with the introduction of a regulation mandating clinical trials for all cell therapies, including those utilizing stem cells, to assess their safety and effectiveness before clinical application. This regulatory framework mirrors international efforts aimed at establishing uniform standards and oversight for stem cell therapies, aimed at safeguarding patient welfare and ensuring their effective utilization across different medical contexts. By implementing these measures, Indonesia aims to foster a responsible and scientifically rigorous approach to utilizing stem cells in healthcare, thereby potentially advancing the country's stem cell research capabilities. Several influential studies have made significant contributions to biomedical research as the most cited journals in Indonesia. Blick et al. (2010) explore the potential of epithelial-mesenchymal transition (EMT) products from basal B cell lines to improve breast cancer outcomes, suggesting novel therapeutic avenues. Hariyadi and Islam (2020) highlight alginate's efficacy in supporting stem cell culture, crucial for maintaining cell viability and functionality in regenerative medicine. Putra et al. (2018) identify that a low dose of TNF-α (5 ng/mL) effectively enables mesenchymal stem cells (MSCs) to suppress inflammation, offering insights into optimizing MSC-based therapies for inflammatory conditions. These studies collectively advance scientific understanding and potential clinical applications in breast cancer treatment, stem cell culture, and MSC-mediated immunomodulation.14

Current Advancements of Cell Therapy in Indonesia

There have been significant developments and studies in stem cell research in Indonesia, spanning from in vitro and in vivo research to exploring innovations in stem cell therapies such as secretome and exosome utilizations. For in vivo studies in Indonesia, there are several studies regarding wound healing using mesenchymal stem cells. There are also in vivo and in vitro studies for wound healing potential using diabetic induced rats. One study highlighted the efficacy of hypoxic conditions in human umbilical cord-derived mesenchymal stem cell conditioned medium (hUC-MSC CM). In vitro experiments confirmed that CM from hypoxic hUC-MSCs facilitated robust wound healing effects, surpassing traditional antibiotic applications. Moreover, in vivo studies provided compelling evidence of enhanced wound closure through re-epithelialization and increased collagen formation. These findings underscore the potential of hUC-MSC CM as a viable therapeutic option for diabetic ulcers15. One study concluded that human-derived mesenchymal stem cells

(MSCs) and platelet-rich plasma (PRP) did not accelerate the epithelialization process in rat burn wound models. However, both treatments significantly improved wound vascularization and cell differentiation. Additionally, another study compared stromal vascular fraction (SVF) and MSCs in promoting wound healing specifically in second-degree burn wounds. It was found that both SVF and MSCs demonstrated effectiveness in enhancing wound healing outcomes.16,17 These findings underscore the diverse therapeutic potentials of MSCs, PRP, and SVF in burn wound management. While MSCs show promise in enhancing cell differentiation, SVF presents a practical alternative for therapeutic applications in burn wound treatment, warranting further exploration and clinical validation to optimize their use in clinical settings. Apart from wound healing, there is also research using dental pulp stem cells (DPSCs) in Indonesia. A study on the differentiation capacity of DPSCs into inner ear hair cells using an in vitro assay marks a preliminary step toward treating sensorineural hearing loss. The research showed that DPSCs successfully differentiated into neural stem cells (NSCs), with 24% of the cells being nestin-positive. This highlights the potential of DPSCs to develop into neural lineage cells, making them promising for regenerative therapies in neural diseases.18

Indonesia is also having recent advances in stem cell research underscore the therapeutic potential of exosome and secretome derived from mesenchymal stem cells (MSCs). First, the finding of exosomes isolated from adipose-derived stem cells using ultracentrifugation, characterized according to MISEV standards, ensure therapeutic efficacy and safety.19 Second, MSC secretome creams containing Interleukin-10 (IL-10) exhibit anti-inflammatory properties, with consistent IL-10 levels across different concentrations.20 Third, exosomes from human umbilical vein endothelial cells (Exo-HUVEC) enhanced cell proliferation, collagen synthesis, and reduced photo-aging effects in UVB-irradiated dermal fibroblasts, suggesting potential for skin regeneration therapy.21 Additionally, MSC secretome showed promise in treating COVID-19-related acute respiratory distress syndrome (ARDS), with further clinical trials and SOP development needed for optimal use.22 These findings underscored the significant promise of stem cell-derived therapies in regenerative medicine. Moreover, collaboration between Indonesia and international researchers and institutions has been instrumental in advancing the field within the country. These partnerships have facilitated knowledge exchange, technology transfer, and joint research initiatives, significantly enhancing Indonesia's capabilities in stem cell science and applications.2

Clinical Applications of Stem Cells

To gather clinical application of stem cells in Indonesia, publication search was conducted on June 14, 2024, in Scopus data base. During the search for articles, the used terms were as follows: "stem cell" OR "stem cells" OR "stromal vascular fraction" AND Indonesia AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (AFFILCOUNTRY , "Indonesia")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")). Based on these keywords, 3,557 articles were initially identified. This number was then narrowed down to 1,930 articles by focusing on studies involving human subjects. After reviewing the titles and abstracts, we considered choosing 39 articles. Furthermore, 32 articles were selected for further study (Figure 1).

We summarized and grouped the data into various conditions/disease, i.e.: orthopedic cases, cardiovascular diseases, hematologic diseases, burns and skin rejuvenation, neurologic conditions, infectious diseases and related conditions, diabetes and related complications, and COVID-19.

Orthopedic cases

The use of mesenchymal stem cells (MSCs) has demonstrated significant potential in various regenerative therapy applications, particularly in treating critical-sized bone defects and other orthopedic conditions. For instance, research on critical-sized defects (CSD) employing a combination of BM-MSCs, hydroxyapatite (HA) granules, and bone morphogenetic protein-2 (BMP-2) indicated substantial improvements in radiological healing and functional outcomes without immunological or neoplastic side effects after one-year follow-up 23. A similar approach was applied to osteofibrous dysplasia, where a combination of BM-MSCs, HA, and BMP-2 successfully generated new normal bone tissue and significantly improved the patient's quality of life without complications after 84 weeks24.

In cases of infected nonunion, the use of UC-MSCs, BMP-2, HA, and the Masquelet technique also succeeded in creating new bone and resolving nonunion without apparent side effects 25. The use of UC-MSCs in combination with HA scaffolds for vertebral body defects showed promising results with effective bone regeneration and no complications after six months 26. The combination of BM-MSCs and HA granules also proved effective in treating long bone nonunion, with patients receiving this therapy exhibiting faster initial radiographic and functional improvements compared to the control group, although similar outcomes were observed after one year of follow-up 27.

Additionally, MSC secretome therapies have shown promising results. For instance, the treatment of knee osteoarthritis

using UC-MSC secretome compared to hyaluronic acid (HA) demonstrated superior clinical improvements, favorable biomarker changes, and no side effects over a five-week interval 28. Similar research using UC-MSCs for knee osteoarthritis also showed significant pain reduction and improved functional scores after six months of follow-up, indicating high regenerative potential of this therapy 29.

Combining surgical techniques with stem cell therapy has also been successfully applied. For example, flexor digitorum profundus tendon injuries repaired with tendon grafts augmented with human amniotic membrane (hAM) and adipose-derived mesenchymal stem cells (ASCs) allowed athletes to return to competition without adhesion complications, demonstrating anti-adhesive properties and accelerated tendon healing 30. A similar approach in managing recurrent patellar dislocation, using a combination of Fulkerson osteotomy, lateral retinacular release, and MSCs implantation, effectively improved cartilage regeneration in patients with chronic patellar instability 31. The use of percutaneous laser disc decompression (PLDD) combined with UC-MSC secretome for spinal cord injury showed significant pain reduction and improved motor strength and postural stability after a one-year follow-up 32.

Therapy for hemivertebra in congenital scoliosis using UC-MSCs also showed promising results, with increased hemivertebra ratio and decreased Cobb angle after three years of follow-up, indicating the potential of this therapy to correct scoliosis curvature and preventing further progression 33. In cases of posterior cruciate ligament rupture, the administration of UC-MSC secretome resulted in excellent functional and radiographic outcomes in the short term, with many patients returning to competitive sports within an average of 25.8 weeks 34.

Overall, the combination of mesenchymal stem cells and secretome with various surgical techniques has demonstrated significant potential in regenerative therapy and the treatment of orthopedic conditions, providing new hope for patients with severe bone and tissue defects. Further studies with larger sample sizes and long-term follow-ups are needed to validate and optimize these approaches.

Cardiovascular Diseases

The combined granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO) based intracoronary infusion of peripheral blood stem cells (PBSCs) in patients with recent myocardial infarction (RMI) has been proven safe and feasible. The therapy showed no procedural complications and exhibited significant improvements in myocardial perfusion and cardiac function over a follow-up period of up to 30 months 35. Another report showed PBSCs therapy in patients with recent myocardial infarction did not significantly alter hemostatic parameters such as platelet aggregation and blood viscosity but did result in meaningful reductions in fibrinogen and CRP levels, suggesting potential benefits in managing hypercoagulability post-myocardial infarction 36.

Combined trans epicardial and transseptal implantation of autologous CD 133+ bone marrow cells during bypass grafting improves cardiac function in patients with low ejection fraction. The cardiac function was ameliorated, including EF, wall motion score index, and scar size proportion, as well as quality of life metrics compared to coronary artery bypass grafting (CABG) alone 37. However, in a randomized, double-blind, placebo-controlled trial study patients with advanced ischemic cardiomyopathy were implanted with autologous bone marrow mononuclear cells resulting in no improvement 38.

Hematologic Diseases

Two multiple myeloma (MM) patients with non-secretory myeloma stage III and IgG myeloma stage II (International Staging System) were treated with induction regimens CyBord until a complete remission followed by autologous bone marrow-derived hematopoietic stem cell (HSC) transplants. Despite complications such as neutropenia, anemia, and mucositis, the patients' conditions improved, leading to their discharge 39.

Burns and Skin Rejuvenation

A comparative study evaluated microneedling (MN) versus fractional CO2 laser (FL) for delivering adipose-derived mesenchymal stem cells (ADMSCs) secretome in facial skin rejuvenation. The findings indicated comparable improvements in skin aging parameters with both methods, emphasizing patient preference and comfort as critical considerations 40. In addition, the use of activated autologous platelet-rich plasma (aaPRP) in treating mid-dermal to full-thickness burns, highlights its potential as an alternative or adjunct to traditional skin grafting methods 41. Additionally, a controlled split-face study examined the combination of fractional erbium YAG laser and topical amniotic membrane stem cell (AMSC)-metabolite product (MP) for facial rejuvenation, demonstrating significant enhancements in skin texture and pore size without serious adverse effects 42. Lastly, an experimental study explored the efficacy of AMSC-MP combined with vitamin E post-fractional CO2 laser for treating photoaged skin, revealing promising outcomes in pore reduction, although with varying effects on wrinkles and UV spots 43. These studies collectively underscore the evolving landscape of stem cell-based therapies and laser treatments

in dermatology, suggesting promising avenues for future clinical applications.

Neurologic Conditions

The use of intraventricular transplantation of autologous bone marrow mesenchymal stem cells (BM-MSCs) in chronic hemorrhagic stroke patients, observing improved NIHSS scores in five out of eight participants without adverse effects over a one-year follow-up 44. Meanwhile, a phase I trial was conducted on intravitreal BM-MSC transplantation in retinitis pigmentosa patients showed no initial improvements in BCVA with stable VF and CST, but transient adverse events. Further research is needed to establish the long-term safety and efficacy of these interventions 45.

Infectious Diseases and Related Conditions

A study of human amniotic membrane stem cell (hAMSC) secretome gel was conducted to reveal its efficacy in treating chronic plantar ulcers in leprosy patients. The results showed that the hAMSC accelerated the wound healing rate with 72.7% of ulcers completely healed and no adverse effects observed 46. Meanwhile, Sirait et al. (2023) conducted a preliminary study on adipose-derived stromal vascular fraction (SVF) for leprosy neuropathy, revealing improvements in sensory functions following SVF injections, despite the detection of mycobacteria in one patient 47. A case report on utilizing minimally invasive surgery combined with umbilical cord mesenchymal stem cell (UC-MSC) secretome for treating cervical tuberculosis resulted in rapid clinical improvement, and underscoring the potential of regenerative strategies in managing infectious diseases 48.

Diabetes and Related Complications

Recent studies have shown promising advancements in the treatment of type 2 diabetes (T2D) and diabetic wound healing. One study investigated the combination of stromal vascular fraction (SVF) and autologous activated platelet-rich plasma (aaPRP), revealing a significant decrease in HbA1c levels post-therapy 49. Another study focused on exosomes derived from adipose stem cells combined with hyaluronic acid (HA), demonstrating improved wound closure rates, tissue regeneration, and reduced inflammation markers 50. Additionally, a Phase 2 clinical trial evaluated a 10% gel formulation of the secretome from human umbilical cord mesenchymal stem cells (SM-hUCMSC) for chronic wounds, reporting accelerated healing without significant adverse effects 51. These findings emphasize the potential of cellular therapies in managing T2D and enhancing chronic wound care, highlighting the importance of further research to validate and expand upon these initial findings.

COVID-19

A double-blind, randomized controlled trial study assessed the safety and efficacy of normoxic allogenic umbilical cord mesenchymal stem cells (NA-UC-MSCs) as adjunctive therapy for severe COVID-19. Despite no significant impact on hospitalization duration or radiographical progression, NA-UC-MSCs notably improved oxygenation indices and suppressed inflammation, suggesting their potential in managing severe COVID-19 cases 52. Furthermore, the DW-MSC infusion in patients with low clinical risk COVID-19 infection through a phase 1 trial was assessed. No severe adverse events were reported, indicating the safety of MSC infusion 53. Moreover, a randomized controlled trial demonstrated that UC-MSCs significantly increased survival rates in critically ill COVID-19 patients, attributed to their immunomodulatory effects in reducing cytokine storms. These studies collectively underscore the potential of MSC-based therapies in mitigating severe COVID-19 outcomes by modulating inflammatory responses and enhancing clinical outcomes 54.

Regulatory Framework in Indonesia

The regulation of cell-based therapies in Indonesia involves three key governmental agencies: the Ministry of Health (MOH), the Indonesian Food and Drug Agency (BPOM), and the National Research and Innovation Agency (BRIN). However, concerns with overlapping responsibilities and ambiguity in function among these agencies led to conflicting regulations 55.

The Minister of Health (MOH), Indonesia has issued regulation No. 32 of 2018 regarding the implementation of stem cell and/or cell therapies. The regulation permits the application of stem cells for therapeutic purposes and health recovery, encompassing the rejuvenation of cells, tissues, and organs in the treatment of both degenerative and non-degenerative conditions. According to the latest regulations, the use of animals, plants, and embryonic stem cells in therapy is strictly prohibited. MOH regulates the entire process of stem cell therapy, from collection, storage, processing, and clinical application. This includes oversight of various administration methods, such as systemic, regional, local, and topical delivery. Interestingly, MOH regulation focuses on standardized therapeutic services for stem cells and includes cell-based therapy trials.

Cell-based therapy trials are translational research and the therapeutic application of stem cells conducted on patients, aiming to continuously improve the quality and effectiveness of therapy through data collection, outcome evaluation, and the development of new procedures based on scientific findings. The cell-based therapy trials offer several benefits, including the development of better therapy standards where data obtained from research can be used to refine procedures and operational standards. Furthermore, it provides evidence-based data from actual therapy outcomes applied directly to patients, fostering innovation and quality improvement in stem cell therapy. Risks and side effects can be closely monitored through multicenter research, helping to identify potential issues early and take necessary mitigation steps to ensure patient safety. However, there are challenges to its implementation, such as resources and prices, which pose issues for healthcare facilities, and there is the possibility of unequal access to research-based therapy, with patients involved in the research receiving advanced treatment while others do not.

Nowadays, stem cell therapy is not standardized yet. Thus, all cell-based therapy trial activities must be conducted as research based cell therapy services within licensed hospitals or their affiliated institutions to ensure compliance with ethical standards and legal requirements. To conduct stem cell therapy, health providers must also meet several requirements such as obtaining a license from the MOH, having adequate human resources and infrastructure, and implementing strict operational standards. Currently, 14 legal hospitals conduct cell-based therapy trials, including:

1. Dr. Cipto Mangunkusumo hospital Jakarta
2. Dr. Sutomo Hospital Surabaya
3. Dr. M Djamil Padang
4. Harapan Kita National Cardiac Hospital Jakarta
5. Dharmais National Cancer Hospital Jakarta
6. Persahabatan Hospital Jakarta
7. Dr. Hasan Sadikin Hospital Bandung
8. Dr. Kariadi Hospital Semarang
9. Gatot Subroto National Army Hospital Jakarta
10. Dr. Sardjito Hospital Yogyakarta
11. Prof. Dr. IGNG Ngoerah Hospital Bali
12. Dr. Wahidin Sudirohusodo Hospital Makassar
13. Dr. Moewardi Hospital Surakarta
14. Prof. Mahar Mardjono National Brain Center Jakarta.

Furthermore, there are ten licensed laboratories certified by the MOH for cell production, including:

1. Regenic Lab, PT Bifarma Adiluhung, Jakarta
2. Prostem Lab, PT Prodia, Jakarta
3. Dermama Biotechnology Lab, Surakarta
4. Asia Stem Cell Center, Jakarta
5. HayandraLab, Jakarta
6. Dr. Cipto Mangunkusumo Hospital Lab, Jakarta
7. Dr. Sutomo Hospital Lab, Surabaya
8. Celltech Stem Cell Lab, Jakarta
9. Cryocord Indonesia Jakarta
10. Tristem Medika Indonesia, Surakarta

Additionally, BPOM Regulation no. 18 (2020) is about the assessment of human cell-based medicines where mass product production can only be performed by a laboratory/production facility that is GMP certified by BPOM 55. Regarding this regulation, BPOM has certified two laboratories: Regenic Lab (PT Bifarma Adiluhung, Jakarta) and Prostem Lab (PT Prodia, Jakarta).

Challenges and Future Directions

In Indonesia, the field of regenerative medicine encounters specific scientific and technical challenges that are crucial to address for the advancement of stem cell therapies. One primary concern is ensuring the safety and efficacy of treatments. Indonesian researchers and healthcare providers must conduct thorough evaluations to verify the safety profile of stem cell therapies, ensuring they do not pose risks such as immune rejection or unintended tumorigenesis. This necessitates robust regulatory frameworks and stringent adherence to ethical guidelines in clinical trials and treatment protocols.14 Regulatory frameworks are very crucial to prevent unproven stem cell therapy, which are flourishing in Indonesia.

Another significant challenge lies in overcoming limitations in current technologies. Indonesia faces obstacles

related to infrastructure, resources, and expertise required for cutting-edge research in stem cell biology and tissue engineering. Improving facilities for stem cell isolation, culture, and characterization is essential to enhance the efficiency and reproducibility of stem cell therapies. Moreover, advancing local expertise in stem cell differentiation techniques and developing tailored therapies that address prevalent health issues in Indonesia, such as cardiovascular diseases and diabetes, are critical priorities.

Addressing these challenges requires collaborative efforts among academic researchers, healthcare professionals, government policymakers, business and industry stakeholders, as well as community and media. Strengthening research capabilities, fostering international collaborations, and promoting public awareness and acceptance of stem cell therapies are integral to realizing their potential in improving healthcare outcomes in Indonesia.

Conclusion

Due to ethical issues, key advancements in stem cell research and therapy focus on the use of adult stem cells for various conditions. Stem cell applications has been done in orthopedic cases, cardiovascular diseases, hematologic diseases, burns and skin rejuvenation, neurologic conditions, infectious diseases, diabetes, and COVID-19, which were conducted as research based cell therapy services. Future prospects for stem cell research in Indonesia are challenging as it is crucial to ensure the safety and efficacy of the treatments. To address these challenges collaborative efforts among academia, government, business, as well as community and media are required.

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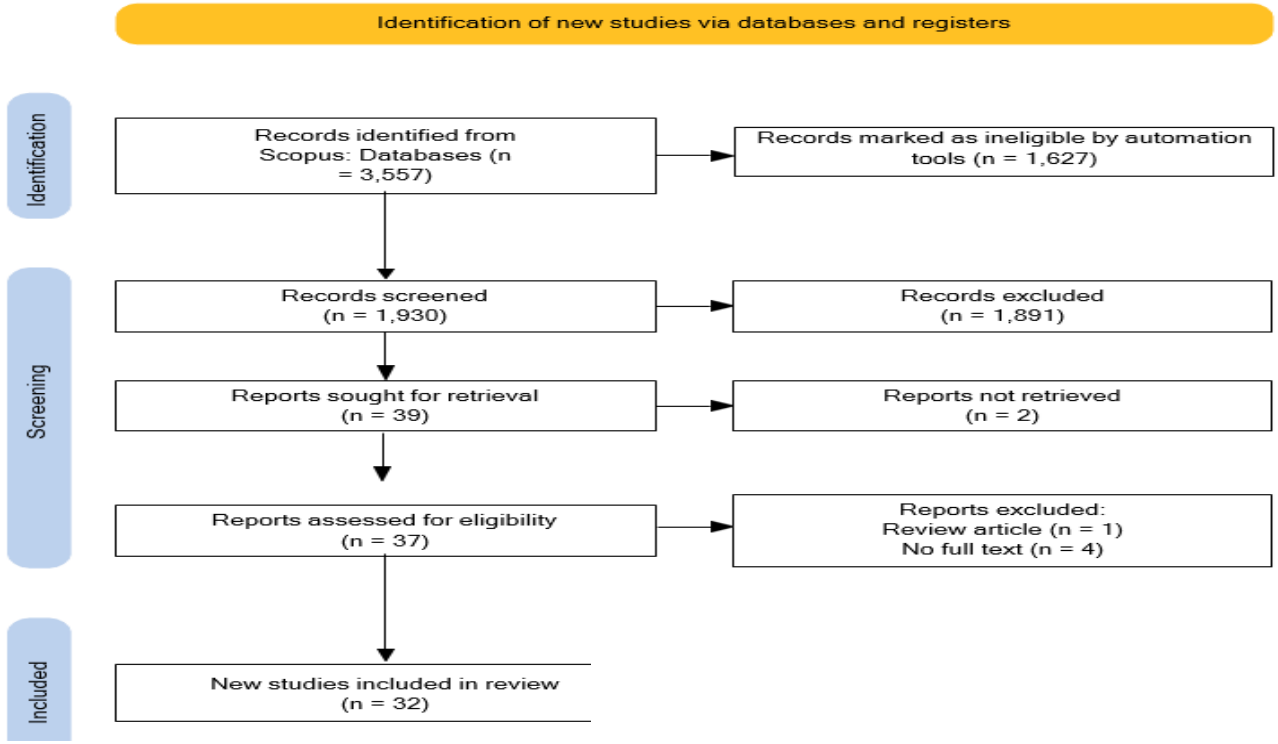

HALAL CERTIFICATION FOR CGT PRODUCT

INDONESIAN PERSPECTIVE

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Basic Concept of Halal

Halal, an Arabic term meaning "permissible," encompasses various aspects of a Muslim's life, particularly regarding diet. The Quranic verse (Quran, chapter 2, verse 168) instructs Muslims to consume halal food, highlighting its importance. This religious obligation extends beyond mere dietary laws to include ensuring the overall quality and purity of products. The concept of halal has gained global recognition as a marker of quality and compliance with Islamic law, benefiting both Muslim and non-Muslim consumers.

Gillani, S. H. B., Ijaz, F., & Khan (2016) note that halal certification has become a universal signal for quality, reflecting the strict adherence to cleanliness, safety, and ethical considerations in product preparation and handling. In regions with significant Muslim populations, the availability of halal products is not just a preference but a necessity. Anwar, M. K., Fahrullah, A., & Ridlwan (2018) emphasize that governments in these nations are responsible for ensuring the availability of halal goods, aligning with the religious and cultural needs of their citizens.

In Indonesia, the LPPOM-MUI (Assessment Institute for Foods, Drugs, and Cosmetics of the Indonesian Council of Ulama) is the authoritative body for halal certification. As reported in 2018, LPPOM-MUI had certified 58,959 halal items out of a total of 655,725 products available in the market, ensuring a significant portion of consumer goods met halal standards (LPPOM MUI, 2018). This certification process guarantees that products adhere to stringent religious guidelines, including the absence of prohibited (haram) substances and adherence to ethical animal slaughtering practices.

Cell and Gene Therapy (CGT) in Indonesia

Stem cell and gene therapy research has seen substantial growth in Indonesia over the past decade. This research spans various applications, including human and animal trials and in vitro studies. Imam Rosadi et al. provide a comprehensive overview of this trend, utilizing bibliometric analysis from Scopus data. Their analysis reveals a consistent increase in stem cell research output, with significant contributions in medical fields such as pharmacology, toxicology, pharmaceutics, biochemistry, genetics, and molecular biology.

The analysis identified 260 relevant articles, with a strong emphasis on terms like "stem cells," "culture," "proliferation," "differentiation," and "tissue engineering." Rantam emerged as a leading author in this domain, reflecting a concentrated effort within certain research groups. This growing body of research underscores Indonesia's commitment to advancing in the field of regenerative medicine, potentially shaping future funding and research priorities (Imam Rosadi et al., 2024).

Halal Certification

Halal certification plays a critical role in ensuring that food and other consumables comply with Islamic dietary laws. According to Nurcahyo, A., & Hudrasyah (2017), this certification involves a thorough assessment

process based on sharia law, conducted by bodies like the MUI (Majelis Ulama Indonesia). The certification process includes detailed evaluations of the entire production chain, from ingredient sourcing and preparation to cooking, serving, hygiene, and labeling.

The presence of a halal mark on a product package signifies that it has successfully passed these rigorous evaluations, offering Muslim consumers assurance of the product's permissibility (Y. Herdiana & T. Rusdiana, 2022). This certification process not only ensures compliance with religious requirements but also enhances the product's overall quality and safety, appealing to a broader consumer base.

Could Cell and Gene Therapy be a Halal Product?

The classification of cell and gene therapy (CGT) as halal hinges on several factors. The US Food and Drug Administration (FDA) regulates various aspects of CGT, including safety testing of human cells, the use of animal materials, donor eligibility, and donor testing (FDA.gov). For CGT to be considered halal, it must adhere to these regulatory standards while also complying with Islamic dietary laws.

This involves ensuring that no haram materials, such as pork or improperly slaughtered animals, are used in the therapy. Additionally, the process must be free from contaminants like ethanol, and the facilities must not handle non-halal materials. By meeting these criteria, CGT products can potentially achieve halal certification, making them suitable for Muslim patients.

Analysis of Global CGT Clinical Trials with or without Halal Certification

Interviews with practitioners in the field of cell and gene therapy highlight the importance of halal certification for Muslim consumers. Despite its significance, not all CGT clinics pursue halal certification. In Indonesia, clinics can operate if they meet the Ministry of Health's standards and Licensing Service requirements, even in the absence of halal certification.

Other Muslim-majority regions, such as Malaysia, Brunei Darussalam, and the UAE, also express concern for halal CGT. However, the specific processes for managing halal certification in these clinics remain unclear. There is a growing need for standardized halal certification protocols for CGT to ensure that these advanced therapies are accessible and permissible for Muslim patients globally.

Overall, the integration of halal principles into the field of cell and gene therapy presents an opportunity to expand the reach and acceptance of these innovative treatments among Muslim populations, ensuring that they align with religious and ethical standards.

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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.

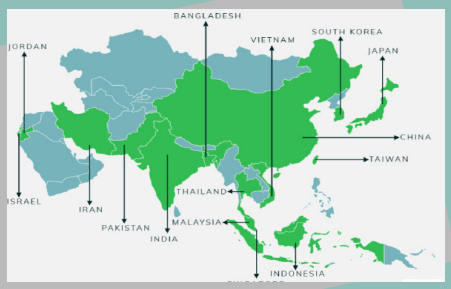
Since its establishment stemming from the ISCT Asian Regional Meeting, ACTO has evolved into a dynamic organization with a broad presence covering 15 regional territories, including Bangladesh, China, India, Indonesia, Iran, Japan, Jordan, Israel, Korea, Malaysia, Taiwan, Thailand, Singapore, Vietnam,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

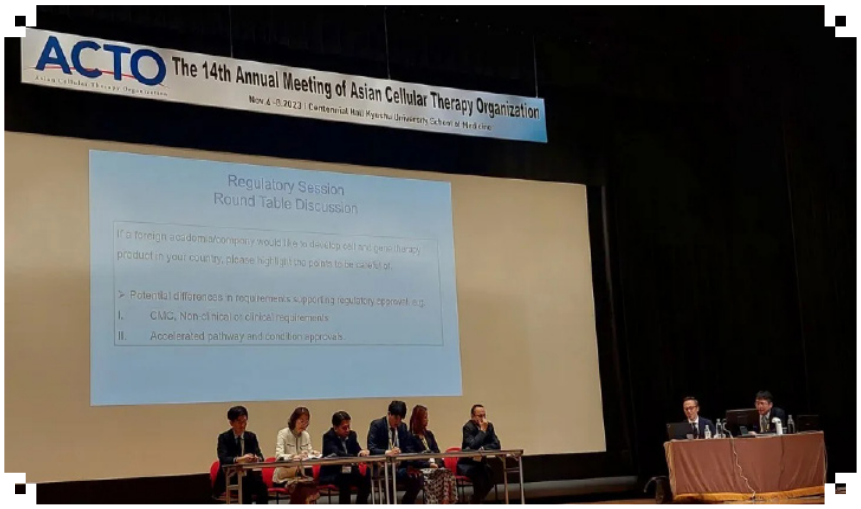
REGULATORY FRONTIERS

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.

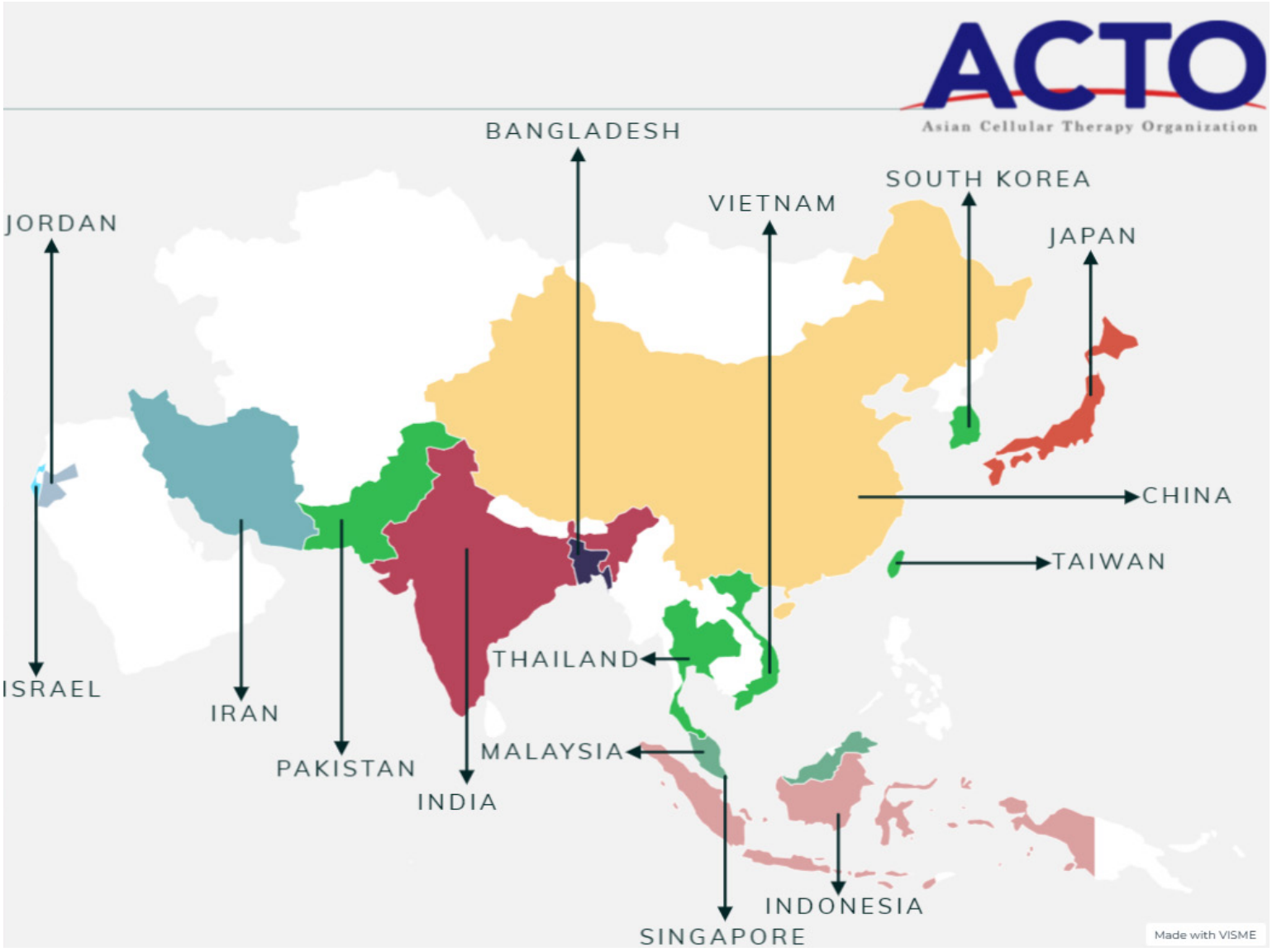
ACTO ACTIVITIES

CHAIRPERSON SHIMOSAKA'S

Meeting for Promoting Collaboration Between Japan & Taiwan In Industry Of Regenerative Medicine

ASH 2023 - CSCO BeiGene

REGIONAL TERRITORIES

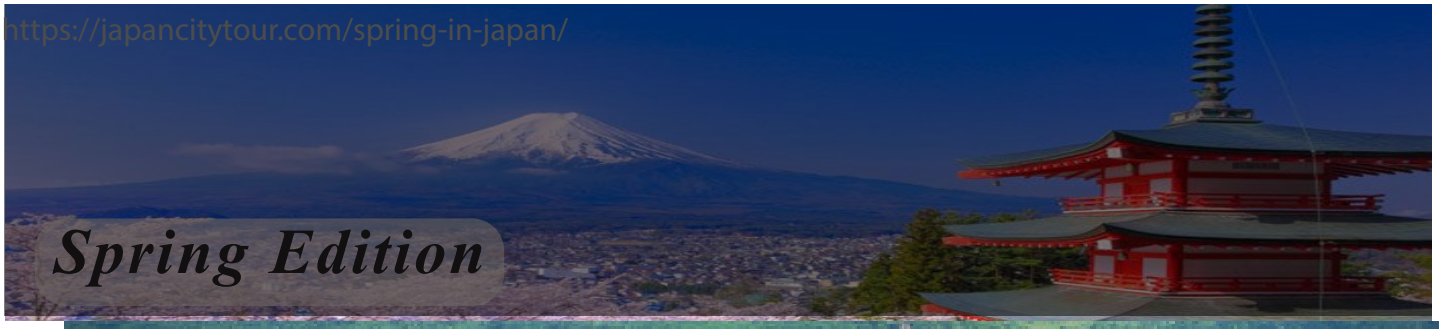


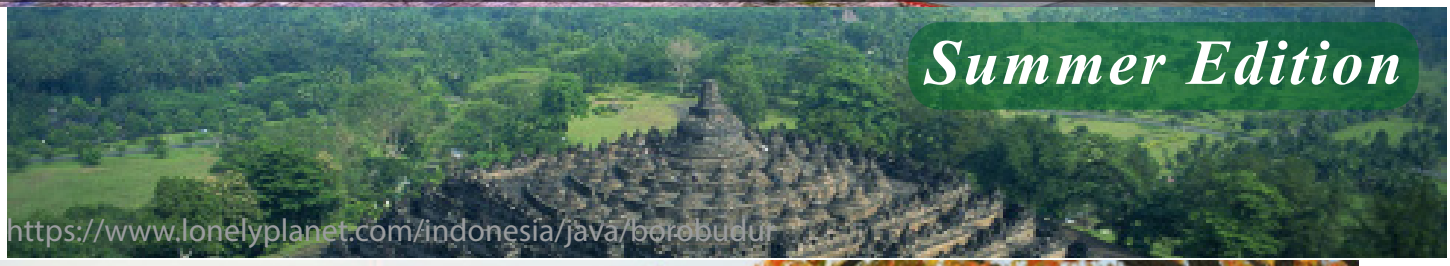
As of the present moment, the Asian Cellular Therapy Organization (ACTO) has seen the enthusiastic engagement of 15 regional territories in its annual meetings. This collective involvement underscores the organization's commitment to fostering collaboration and knowledge exchange among diverse regions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

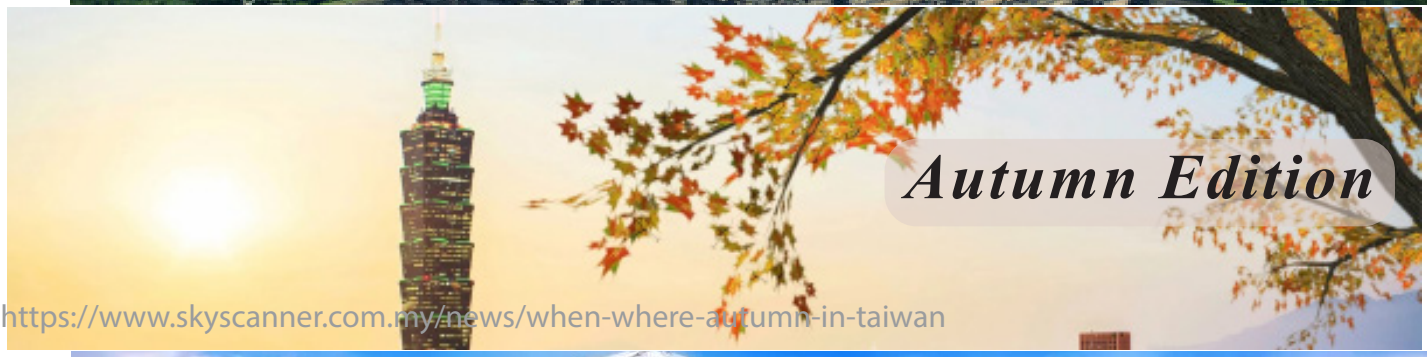
NEWS

THE ACTO TIMES PRESENTING

ACTO NEW SEASONAL E-MAGAZINE







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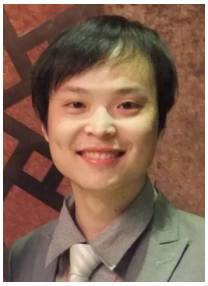

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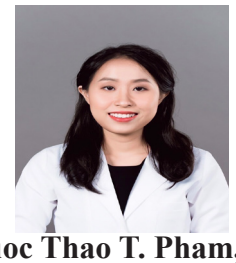

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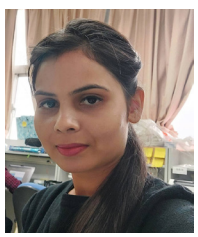

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RECRUITMENT

"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.

REGIONAL ASSOCIATE EDITOR

- Bangladesh
- China
- India
- Indonesia
- Iran
- Japan
- Jordan
- Israel
- Korea
- Malaysia
- Taiwan
- Thailand
- Singapore
- Vietnam
- Pakistan
- USA
- Europe
- Australia
- New Zealand
- South Africa

ACADEMIC ASSOCIATE EDITOR

1. Cell and Gene Therapy (CGT)
   - Cell Drug Development
   - Clinical Trial
   - Gene-modified Cell Therapy (CAR-Cell)
   - Immune Cell Therapy
   - Secretome / Exosome
   - Somatic Cell therapy
   - Stem Cell Therapy
2. Industry Properties
   - Manufacture, Production, Auto-machine
   - Regenerative Therapy
3. Regulation
4. Talent Education
5. Global Connection
   - Global Symposium
   - Global Investment Bio

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- Nova Yuli Prasetya Budi, MD, PhD (Indonesia)
- Dyah Ika Krisnawati, RN, PhD (Indonesia)

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