出國報告（出國類別：開會）

參與 2024 年北美生物科技展 (BIO 2024)「細胞與基因治療法規論壇」

服務機關：衛生福利部
姓名職稱：劉越萍司長
派赴國家/地區：美國/聖地牙哥
出國期間：113 年 6 月 1 日至 6 月 5 日
報告日期：113 年 7 月 3 日

摘要

全球最大規模生技展會「BIO International Convention」(BIO 2024)於113年6月3至6日在美國加州聖地牙哥登場。

台灣生物產業發展協會今年特別與 BIO 大會主辦單位共同規劃辦理「細胞與基因治療法規論壇」，並特地安排於 BIO 2024 大會開幕第 1 天舉辦，分享臺灣、日本及亞洲經驗，以廣宣我國細胞治療相關政策與現況，加大國際能見度並強化國際交流、合作與社群互動。

此場會議由台灣生物產業發展協會秘書長林治華主持，以細胞與基因治療法規為焦點，邀請臺灣衛福部醫事司司長劉越萍、日本醫藥品醫療機器綜合機構(PMDA)細胞和組織產品辦公室審查主任丸山良亮(Yoshiaki Maruyama)分享臺灣、日本最新法規政策及展望，同時也邀請臺灣安美睿(Amarex Taiwan)營運長何佳樺(Maggie Ho)分享加速細胞與基因療法(CGT)臨床試驗的關鍵，以及著名跨國健康產業智庫 Crowell & Moring International(CMI)顧問公司的全球生命科學主席 Joseph Damond 剖析 CGT 的國際產業趨勢與待解挑戰。

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壹、目的

近年來，亞太地區細胞和基因療法的發展與成長非常迅速，僅次於北美。亞太地區監管機關意識到此一生技研發為未來新興趨勢，已開始著手製定相關管理規範和配套措施以因應此一發展浪潮；另一方面，監管機關與公衛醫療體系也期盼在品質、安全及療效的前提下，運用生技科學與有效率的法規規範及審查制度，使病患能及早使用創新醫療及產品，以嘉惠患者。所以在此次BIO 2024大會，台灣生物產業發展協會與 BIO 大會主辦單位共同規劃辦理以「“Patients Wait Less”-Streamlining Regulatory Pathways for Cell and Gene Therapies in Asia-Pacific Region」為主題之大會官方論壇，進行討論亞太地區不同市場先進療法的監管環境、審查與查驗登記程序、再生醫療的法規制定及效率促進方案等，並探討政策制定者和監管機關如何推動再生醫療發展。

本次會議著重於比較和討論亞太地區不同市場細胞治療、基因治療的管理概況，以及現行的上市審查程序，並邀請日本和臺灣再生醫療主管機關、專家分享其相關法規規範、觀點及經驗等。同時邀約第三方講者，分享和討論對細胞治療、基因治療的未來需求，及後續建立相關管理制度與框架之見解、經驗和意見。最後藉由問答，與觀眾進行互動討論，以全面涵蓋再生醫療中未滿足的需求、機會、挑戰和解決方案等關鍵觀點。

臺灣衛生福利部醫事司劉越萍司長受邀在「細胞與基因治療法規論壇」上分享臺灣細胞治療最新法規政策及展望，以廣宣我國細胞治療相關政策與現況，加大國際能見度並強化國際交流、合作與社群互動。

貳、過程

一、行程簡介

日期	行程
6/1(六)	搭機前往：臺灣桃園→美國洛杉磯/聖地牙哥
6/2(日)美國時間	Registration/準備作業
6/3(一)美國時間	15:00-16:00 BIO Session： 「細胞與基因治療法規論壇」-劉越萍司長擔任講者
6/4(二)美國時間-6/5(三)	搭機返國：美國聖地牙哥/洛杉磯→臺灣桃園

二、論壇簡介

(一)論壇時間：美國時間 6 月 3 日下午 3 時至 4 時 (大會開幕第 1 天)

(二)論壇主題：“Patients Wait Less”-Streamlining Regulatory Pathways for Cell/Gene Therapies in Asia-Pacific Region

(三)論壇摘要：

1.臺灣及日本分享目前兼顧病患需求及科學嚴謹之細胞/基因治療法規特色。

2.在臺灣及日本等亞洲國家有經驗之國際 CRO 分享亞洲經驗。

3.總部設於美國之國際 NGO 智庫組織分享全球趨勢觀察。

三、演講摘錄

此場會議由台灣生物產業發展協會林治華秘書長主持。林治華秘書長開場指出，細胞/基因治療因為具有再生與修復的能力，在治療某些疾病上具有巨大潛力，但細胞治療有別於傳統小分子和生物製劑，因是透過活體細胞來發揮藥物機制，在開發上會涉及醫師、藥廠、法規與製造環境，是相當具有挑戰的療法，因此各國主管單位都在不斷優化其管制模式。

講者 1：臺灣衛福部醫事司劉越萍司長分享臺灣細胞治療法規發展的現況

(一)臺灣發展細胞療法幾個關鍵，包括即將面臨超高齡社會，以及 2015 年八仙樂園塵爆，當時臺灣的傷患使用日本的細胞治療技術來移植皮膚頗具成效，也提高了民眾對此需求的意識。

(二)臺灣自 2017 年起陸續發布相關法案，包括細胞及基因治療產品管理法(草案)、2018 年發布特管辦法開放六項細胞治療、2022 年訂定再生醫療雙法草案等。特管辦法的推動最早是來自病友發起的聯署，當時只花一週左右時間就達成 5,000 多人連署。臺灣政府非常重視人民需求，進而督促主管單位開始規劃法案，同時也向立法最早的日本學習。

(三)截至 2023 年 12 月 31 日，特管辦法總收案人次共有 1,398 人，其中 1,138 名接受自體免疫細胞治療。在最新公布的成效報告中，共有 538 名患者完成治療、101 人未完成完整療程、272 人未接受治療。依據目前完成追蹤、可分析的數據來看，癌症患者在接受自體免疫細胞治療後，平均可延長存活將近 1 年。

(四)呼應林治華秘書長提到細胞治療產品的製造環境與品質管理問題：衛福部在 2023 年推動的再生醫療雙法草案中，保留特管辦法中醫療機構品質管理部分，更強化再生醫療生技醫藥公司細胞製備場所的管理作為；再生醫療雙法的通過也將嘉惠病患，促進生技產業發展。

(五)臺灣發展再生醫學，除了加速創新技術開發、確保治療和研究品質之外，也要透過患者治療後追蹤，縮小產業內資訊差距，同時刺激患者需求，以促進整體產業活絡。

講者 2：日本醫藥品醫療機器綜合機構(PMDA)細胞和組織產品辦公室審查主任丸山良亮(Yoshiaki Maruyama)分享日本細胞/基因療法開發現況

(一)目前日本再生醫學技術與產品是透過雙法來監管，其一是《再生醫療安全確保法(Safety Act)》，主要是針對使用加工細胞的醫療技術，因安全性和有效性尚待確定，屬於學術研究或醫療保健或臨床研究目的產品進行規範。第二是《藥機法(PMD Act)》，針對具有商業目的的再生/細胞治療產品，規範其生產和銷售。

(二)在《再生醫療安全確保法》規範下，日本根據再生醫學技術的風險高低，分類成第一、二、三級，並給予不同的監管措施。截至 2023 年 12 月底，在醫療保健上依風險高低，第一級(風險最高)共有 7 件申請、第二級(中度風險)1,571 件、第三期(低度風險)3,898 件；在臨床研究上，第一級則有 16 件、第二級 43

件、第三級42件。目前日本也朝向規劃把體內基因治療納入《再生醫療安全確保法》，而他本人正參與該法規的制定。

(三)有關《藥品和醫療器材法》，從2014年開始，已累積約240例案件，PMDA審查通過的細胞/基因治療產品目前約 20 件，其中細胞治療最多，其次是體外基因治療，最後是體內基因治療。

(四)目前許多國家都在推行「有條件的批准」(conditional approval)，尤其是美國。日本也在治療方式有限情況下，透過有條件批准方式，讓患者提早接受治療，同時也進行上市後的療效及安全性追蹤。PMDA就將三種治療角膜輪部幹細胞缺損(LSCD)，皆為幹細胞療法的Nepic、Ocural、Sakracy進行上市後對照性的臨床研究，該研究有助於了解再生醫療產品臨床設計，可為未來臨床試驗設計，或下一個適應症提供更靈活的建議。

講者3：臺灣安美睿(Amarex Taiwan)營運長何佳樺(Maggie Ho)分享如何透過創新的方法設計一個成功的基因與細胞療法臨床試驗

(一)首先，從細胞與基因療法的機構設址與研究領域統計來看，可以發現美國是開發細胞與基因療法最多的地區。有趣的是，在美國比較多人開發基因療法，而亞太地區則較專注於細胞療法。

(二)臨床試驗最重要的關鍵考量是安全性。在基因療法中，需考量是否影響受贈者的基因體，或是造成無法控制的生物反應與免疫反應，或是對基因療法載體產生免疫反應。在細胞治療中，則是注重細胞是否會分化成非原先預定的細胞類型、細胞移至非目標位置、移植物抗宿主疾病(GvHD)等等。

(三)早期應將所有風險納入臨床試驗設計規劃中：很多再生療法都是用於治療罕見疾病，患者數量少，其樣本數難以適用於傳統的臨床試驗臂(clinical trial arm)設計。因此可透過在隨機分組的階段，指定患者基因型或使用共變異數(covariance)分析，並可搭配虛擬患者追蹤，可以對小規模的患者族群進行長期追蹤。

(四)創新細胞與基因療法的臨床試驗設計有三大關鍵，包含數位化轉型、了解各國法規差異以及重視創新再生療法的新穎性和風險平衡，因此建議早期就與主管

單位接觸或尋找經驗豐富的合作夥伴，以加速再生療法的臨床進展。

講者 4：跨國健康產業智庫 Crowell & Moring International(CMI)顧問公司的全球生命科學主席 Joseph Damond 分享基因和細胞療法的全球變革

(一)基因和細胞療法正在改變現今的醫療保健，並為罕見、難治的疾病帶來曙光。CGT 領域也正蓬勃發展。根據統計，全球 CGT 臨床試驗在過去 5 年已啟動 3,285 項，光是 2023 年就有 631 項啟動。自 2010 年以來，CGT 臨床試驗數量年增長率已達 20~25%，市場估值將從 2023 年 115.7 億美元，至 2032 年成長到 409.8 億美元，年均複合成長率(CAGR)為 15.09%。值得注意的是，市場份額最大的國家仍是美國，營收占比為 48.3%，第二為亞太地區，占比 21.1%。

(二)近 10 年亞太地區臨床試驗數量中，中國臨床試驗數量占比已從 14%，成長到 42%，是全亞太地區成長最多。

(三)目前 CGT 臨床試驗最熱門的前三大領域分別為：血癌、實體腫瘤、自體免疫疾病。不過即便 CGT 已成熱門領域，但是仍有幾項關鍵因素尚待突破，包括監管法規、基因改造引起的道德風險、治療費用高居不下，以及 CGT 產品涉及複雜的生物材料難以申請專利，並較難在世界各地布建基礎設施與物流等。

參、心得及建議

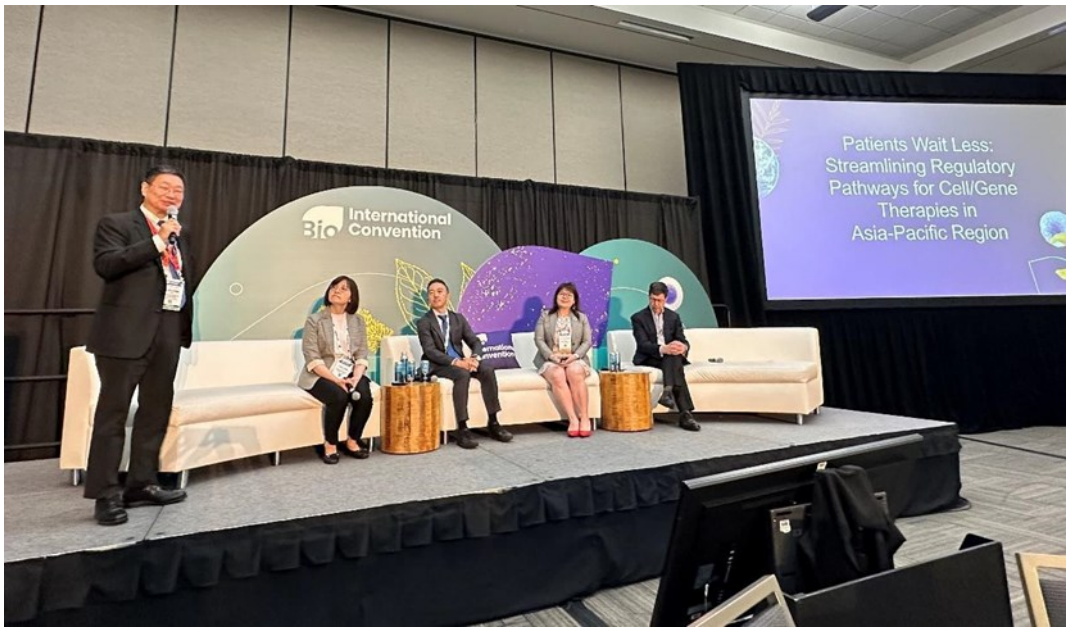
全球規模最大之生技展會「BIO International Convention」(BIO 2024)於 113 年 6 月 3 至 6 日在美國加州聖地牙哥會議中心盛大舉行。此次很榮幸受邀在大會第 1 天下午的會議上分享「臺灣細胞治療現況與展望」，藉此一機會讓國際看見臺灣在再生醫療領域的發展與能量，也同步掌握日本、亞洲地區及全球生技發展最新趨勢。

新興生醫科技發展的大躍進，讓難治疾病獲得一線生機!對於傳統治療方式無效的急重症病人，再生醫療提供另一治療選擇權。鑑於再生醫療之異質性、特殊性及治療複雜性，此生機伴隨高風險及不確定性，因此落實管控新醫療技術、細胞操作過程及最終成品的品質，確保病人就醫安全，並審慎評估其臨床治療效果，確保病人接受再生醫療所獲利益高於其風險，是主管機關應當之責。

為此政府部門積極前進，終於再生醫療雙法在朝野黨團、公私團體及行政部門多年來的共同努力之下，於 113 年 6 月 4 日由立法院完成三讀，是確保醫療機構執行再生醫療之安全及品質、維護病人接受治療之權益的重大里程碑。再生醫療雙法的通過，除促進再生醫療領域發展，亦加速再生醫療研發成果擴大應用至臨床醫學，並順應當前醫療發展趨勢，符合實務管理需求。臺灣擁有優秀臨床醫療優勢，再生醫療法規制度的完善，將有利我國生技產業爭取打入國際供應鏈及擴展市場商機。

肆、附錄

一、會議照片



▲BIO 大會論壇 Cell and Gene Therapies session

▲BIO 大會論壇 Cell and Gene Therapies session 講員合影

資料來源：社團法人台灣生物產業發展協會

二、會議主持人及講員名單

角色	姓名	職稱	單位
主持人	林治華 (Wallace Lin, Ph. D.)  	秘書長	台灣生物產業發展協會
林治華博士，台灣生物產業發展協會（Taiwan BIO）秘書長，擁有30年的科技管理、監管和政府政策經驗。他曾擔任臺灣行政院科技會報辦公室生物科技、醫療、醫藥和農業主任，致力於促進臺灣生物科技的發展。林博士也曾擔任臺灣藥品、醫療器材、保健食品和健康技術評估的監管機構財團法人醫藥品查驗中心（CDE）的代理副執行主任。 他曾是臺灣經濟部的全職科技顧問之一。林博士是SynNovate的創始人兼執行長，這是一家以科技為基礎，在台灣成立並在亞洲有業務的公司。林博士曾是工業技術研究院聯合化學研究所特殊高分子實驗室主任，以及國立交通大學和中原大學的生物科技兼任副教授。			
講者1	劉越萍 (Yueh-Ping Liu, M. D., LLM) 	醫事司司長	臺灣衛生福利部

劉越萍博士目前擔任臺灣衛生福利部醫事司司長。她的工作職責包括制定與醫療保健相關的政策和法律、制定國家醫療服務的戰略規劃和指導，以及推動醫療保健領域的生物技術創新。同時她也是國立臺灣大學醫學院附設醫院急診部的主治醫師。

作為一名醫生，她是臺灣兒科急診醫學的先驅之一。她為改善緊急醫療系統服務質量，尤其是對兒童的服務，以及提高公共服務效率做出了貢獻。同時為了減輕各利害關係人之間的醫療法律衝突，她於2016年獲得法學碩士學位。

講者2	丸山良亮 (Yoshiaki Maruyama, Ph. D.) 	細胞和組織產品辦公室主任(Office Director, Office of Cellular and Tissue-based Products)	日本醫藥品醫療機器綜合機構(Pharmaceuticals and Medical Devices Agency, PMDA)

Yoshiaki Maruyama博士目前是日本醫藥品醫療機器綜合機構（PMDA）細胞和組織產品辦公室的主任。2008年，Maruyama博士加入PMDA，成為合規與標準辦公室的一名官員，同時也擔任日本藥典的秘書工作直至2012年。Maruyama博士負責的工作很廣泛，從細胞/基因治療產品、組織製品到生物製品的審批審查，以及後續市場監控。

Maruyama博士參與領導日本厚生勞動省（MHLW）和PMDA的“the development of ICH guidelines and Annexes on the Evaluation and Recommendation of Pharmacopoeial Texts for use in the ICH Regions (Q4B)”發展主題。

在加入PMDA之前，Maruyama博士曾是加拿大卡爾加里大學的研究員（2001年至2005年），以及日本東京國立神經精神病中心（NCNP）的研究員（2005年至2008年）。

講者3	何佳樺 Chia-Hua (Maggie) Ho, DPhil 	營運長 (Chief Operating Officer)	臺灣安美睿(Amarex Taiwan, LLC)
作為Amarex Taiwan的首席運營官，Maggie負責跨太平洋地區的業務運營，包括亞太地區的監管提交、臨床運營、業務拓展和客戶服務。Maggie在臨床研究和制藥產品開發方面擁有超過15年的經驗，因此具備豐富的專業知識。作為在美國接受培訓的監管專家，Maggie擅長小分子藥物、生物製品、植物製劑和器械制定細則的監管批准策略，及應對美國和亞洲的產品開發複雜性。她也在細胞和基因治療領域，特別是在美國和亞太地區的各種市場中，對先進療法監管背景有其深入洞察。 Maggie在化學方面獲得了牛津大學的博士學位，具備實踐經驗與扎實的科學研究基礎。她致力於推進該領域的知識，並在牛津大學、麻省理工學院等知名機構做過研究，並發表在《自然》、《自然化學生物學》、《美國國家科學院院刊》和《PLoS病原體》等知名期刊上。			
講者4	Joseph Damond 	Chair of Global Life Sciences)	Crowell & Moring International (CMI)

作為CMI全球生命科學團隊的全球主席，Joseph Damond協助客戶進入及擴大全球市場，範疇涵蓋醫療保健、生命科學、醫療器械和健康公司。Joseph與醫療保健行業的領先客戶合作，推動醫療政策倡議，並應對不斷發展的全球政治和監管環境。他還專注於跨國公司面臨的國際貿易和投資挑戰。作為新興技術問題的公認領導者，Joseph利用他三十年的經驗，就標準、最佳實踐、立法、法規和公共準備提供見解。

在加入CMI之前，Joseph是Edelman Global Advisory的醫療政策主席。Joseph還曾擔任生物技術創新組織（BIO）的副首席政策官兼執行副總裁，負責制定該行業協會在醫療保健、經濟和貿易問題以及外國政府關係政策方面的全球政策戰略。

在BIO工作之前，Joseph擔任輝瑞公司的國際政府關係副總裁，管理其國際貿易和商業問題，包括領導行業努力加強進入市場和知識產權（IP）條款在美韓自由貿易協定中的規定。在輝瑞公司之前，他在美國製藥研究與製造商協會（PhRMA）擔任國際政府關係副總裁，領導亞洲和全球市場進入計畫，並制定行業在美澳自由貿易協定中市場IP和進入條款的成功策略。

Joseph在Office of the U.S. Trade Representative工作了十二年，擔任過多個職務，包括美國貿易代表（USTR）的特別經濟助理、普惠制度執行主任以及亞太副助理貿易代表，負責東南亞和亞太經濟合作組織（APEC）。他是2000年完成歷史性美越雙邊貿易協定的首席談判代表。在加入USTR之前，Joseph是美國商務部的貿易政策官員。他本科畢業於喬治城大學外交學院，研究生學位則為普林斯頓大學公共和國際事務學院。

三、會議講者簡報

(一)臺灣衛生福利部醫事司劉越萍司長

題目：Current Status and Outlook of Cell Therapy in Taiwan

(二)日本醫藥品醫療機器綜合機構(PMDA)細胞和組織產品辦公室審查主任丸山良亮(Yoshiaki Maruyama)

題目：Current Status on Cell/Gene Therapy Development in Japan

(三)臺灣安美睿(Amarex Taiwan)營運長何佳樺(Maggie Ho)

題目：Driving Success in CGTs Clinical Trials with Innovative Approaches

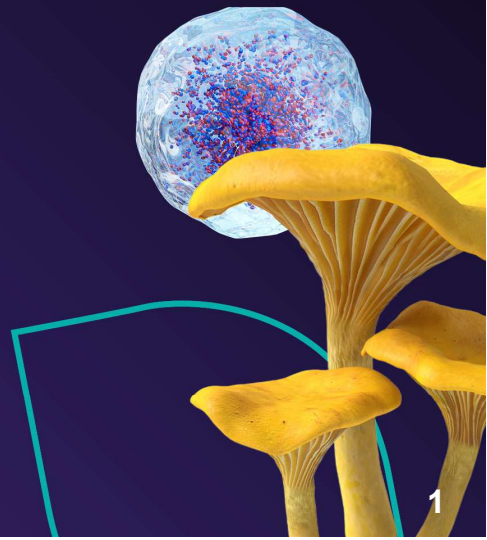
(四)Crowell & Moring International(CMI)全球生命科學主席 Joseph Damond

題目：Cell and Gene Therapies:Global Outlook and Emerging Policy Issues

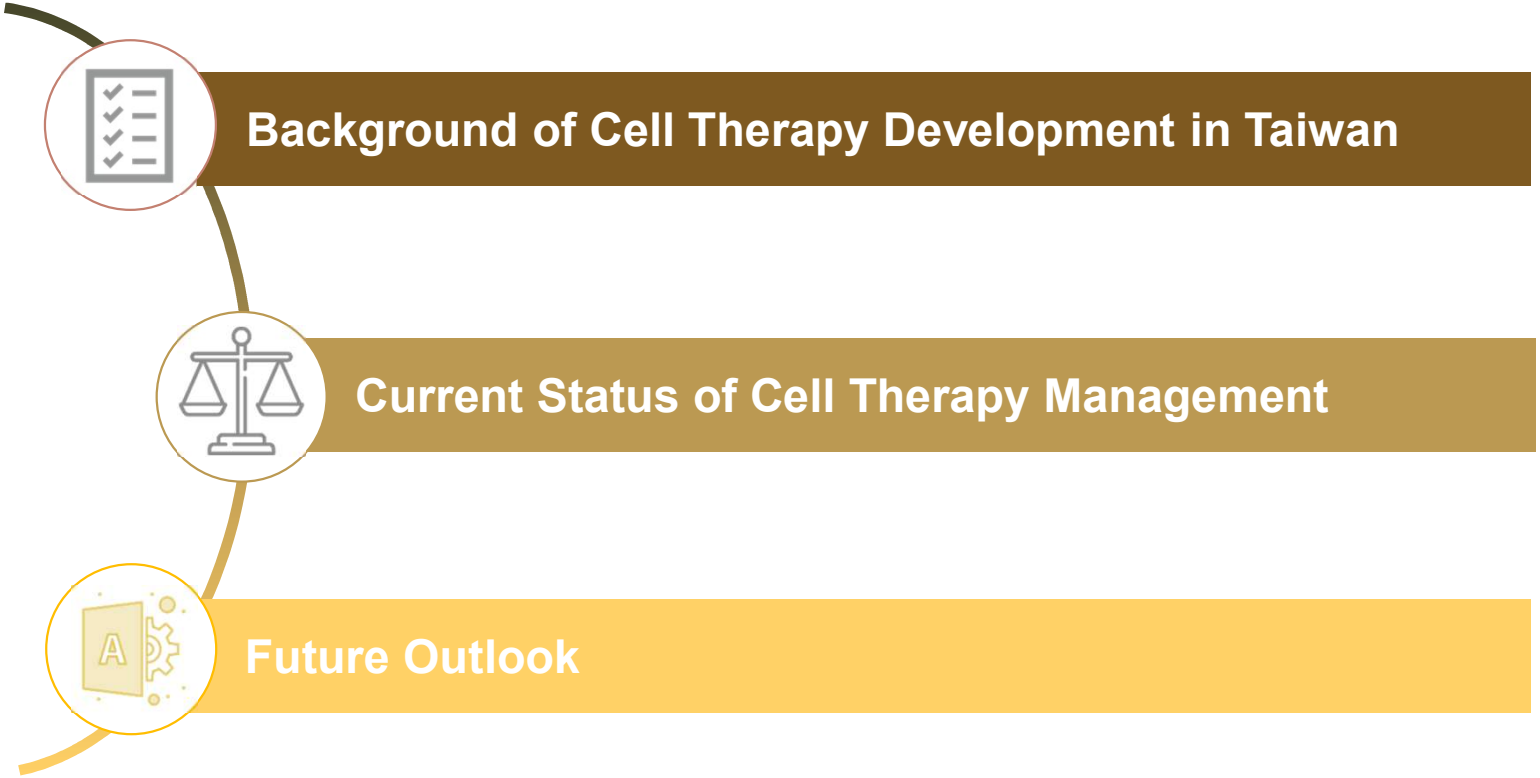
Current Status and Outlook of Cell Therapy in Taiwan

Yueh-Ping Liu, MD, LLM
Director-General,
Department of Medical Affairs,
Ministry of Health and Welfare

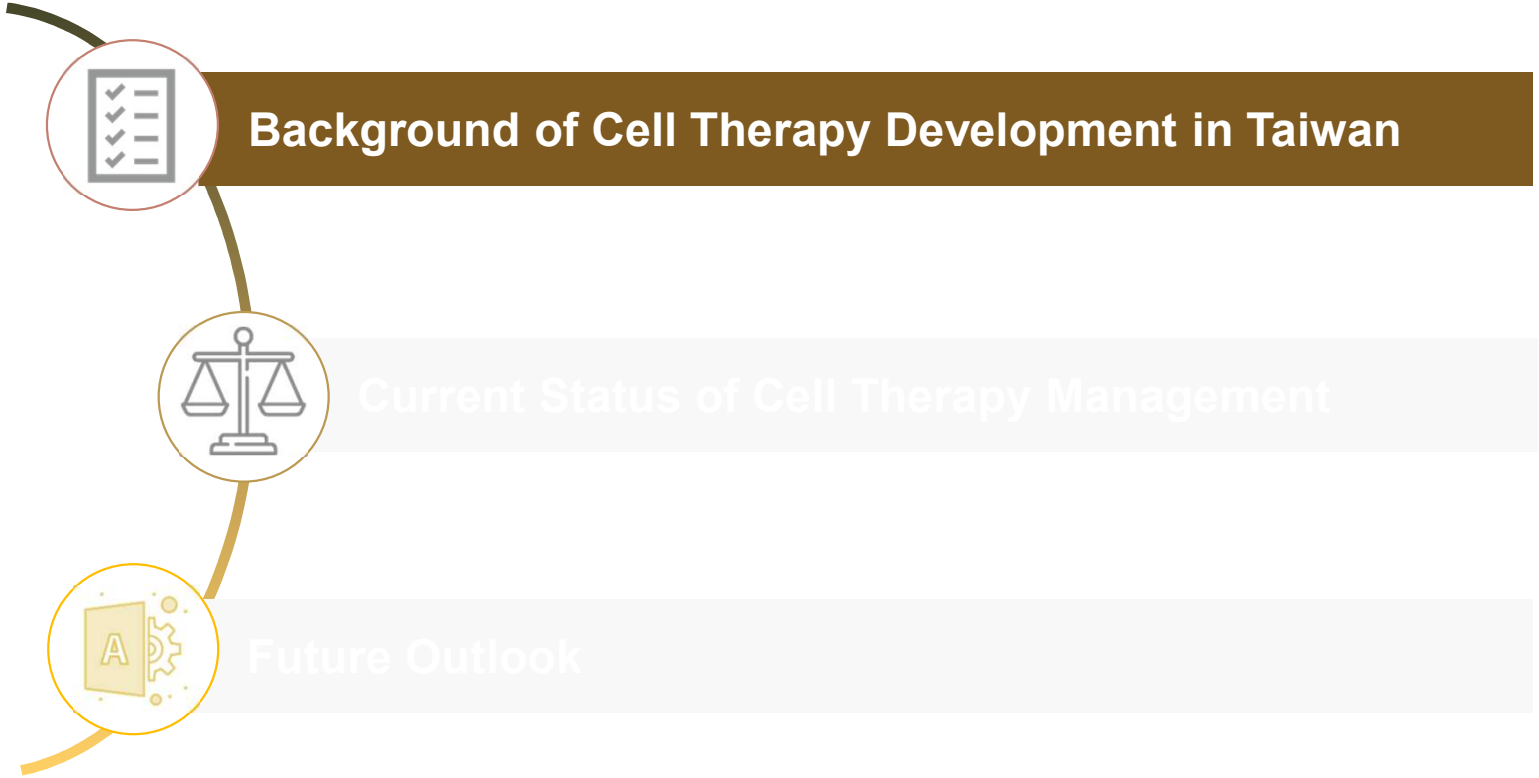
June 3, 2024



Outline


Background of Cell Therapy Development in Taiwan
Current Status of Cell Therapy Management
Future Outlook

Outline


Background of Cell Therapy Development in Taiwan
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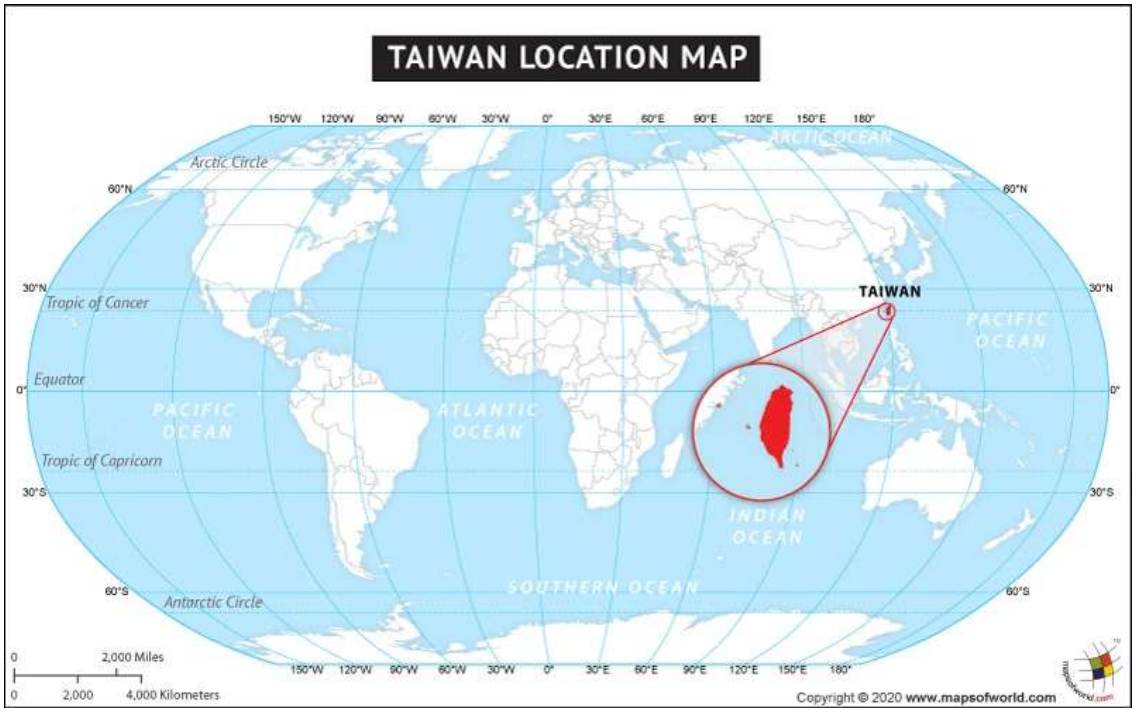
Future Outlook

Brief introduction of Taiwan



- Situates in East Asia at the northwestern edge of the Pacific.
- Total population (April,2024): 23,415,100
  - In 1993,Taiwan officially became an “aging society” .
  - In 2018, Taiwan officially became an “aged society”.
  - By 2025, Taiwan will become a “super-aged society”.
  - In 2022, Taiwan recorded its lowest-ever birth rate of 0.89 births per woman, which is far below the population maintenance rate of 2.1 births per woman.
- The life expectancy (2023) : 81.04 years
- GDP per capita (2022): USD 32,679

Taiwan‘s Ministry of Health and Welfare (MOHW) Actively Legislates to Address Cell Therapy Needs

Demands from civil society

Legislation by MOHW

2003

Implementation of the “Regulation Governing the Application of Specific Medical Examination Technique and Medical Device (RASMET)“

Providing legal protection and institutional support for the sound development of the industry then

2015

On 27 June of 2015, the Formosa Fun Coast dust explosion incident caused 497 injured (15 of the 497 injured had died), Taiwanese patients used Japanese artificial skin grafting technology, raising public awareness of the need for cell therapy.

In October of 2015, Citizens proposed to "submit the amendment bill for cancer immunotherapy to the Legislative Yuan by the end of December of 2015 and accelerated the introduction of new cancer drugs" on the "Public Policy Online Participation Network Platform" .

2017

Announcement of the *Cell and Gene Therapy Product Management Act* (Draft)

Ensuring the safety and efficacy of cell and gene therapy products

2018

RASMET amendment

This opens up six areas of cell therapy technology such as autologous immune cell therapy for cancer patients who failed standard treatment .

2022

Announcement of the *Regenerative Medicine Dual Laws*

Replacing lower-level regulations with higher-level laws (RASMET) to offer more comprehensive legal frameworks and standards

* Image source for Formosa Fun Coast explosion: United Daily News archives

Taiwan's Ministry of Health and Welfare (MOHW) Actively Legislates to Address Cell Therapy Needs

Public participation in proposing policy needs

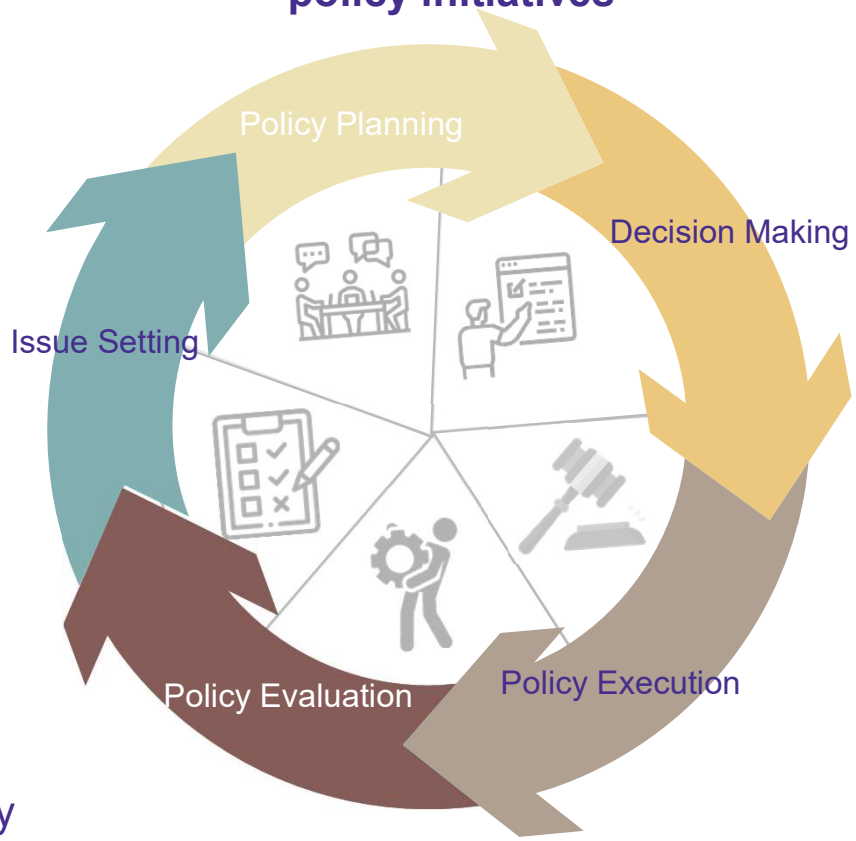
Public Policy Online Participation Network Platform

Taiwan Government 's pioneering online proposal mechanism

October 2015: "Idea Submission" proposed to "Submit the amendment bill for cancer immunotherapy to the Legislative Yuan by the end of December of 2015 and accelerated the introduction of new cancer drugs"

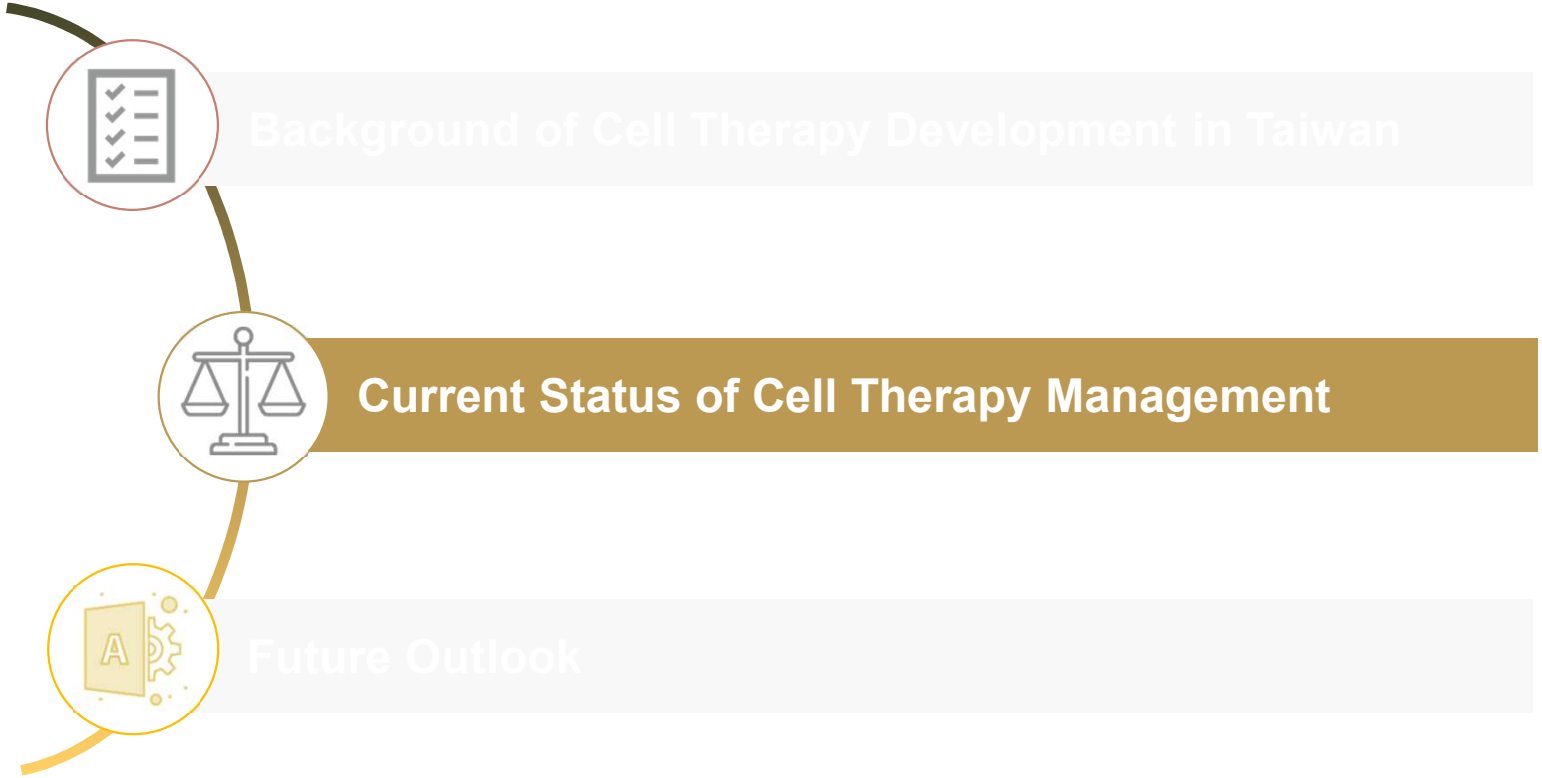
Citizens proposed specific treatment needs

Establishing systems driven by policy initiatives



Patient's Right to Try

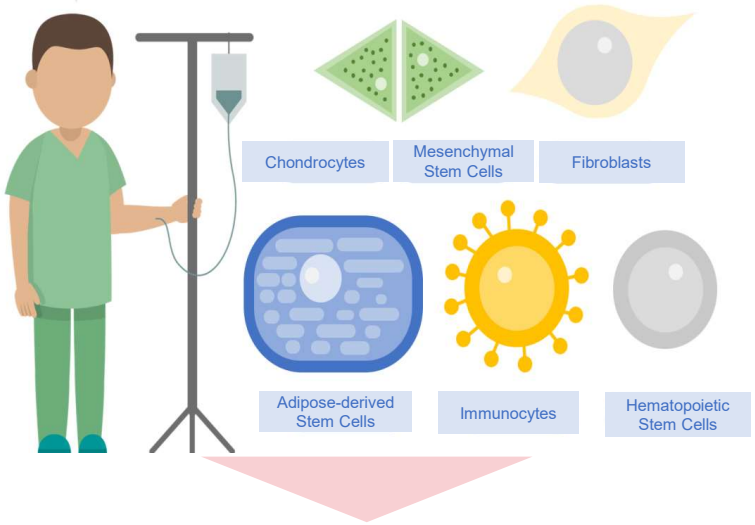
Outline


Background of Cell Therapy Development in Taiwan
Current Status of Cell Therapy Management
Future Outlook

Implementation Status of Cell Therapy Technology in Taiwan

Demand for Cell Therapy in Taiwan

6 Cell Therapy Technologies Approved

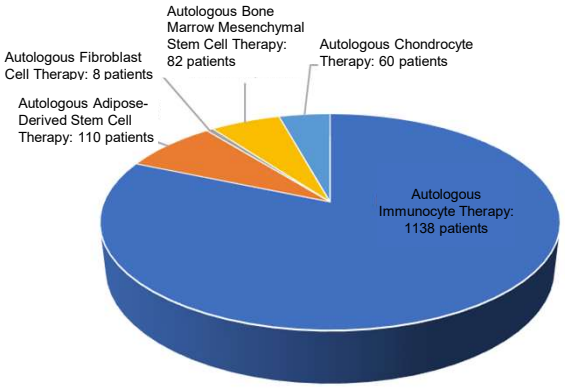


- Considering **autologous use, low risk, and certainty of safety**
- **As of December 31,2023, total of *502* cell therapy technology implementation plans applied to MOHW**

Overview of Cell Therapy Technology Implementation in Taiwan

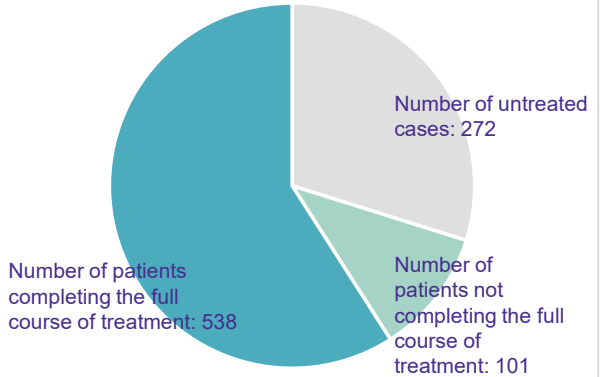
As of December 31, 2023, a total of **305** cell therapy technology implementation plans have been approved, with the main treatment targets being tissue repair and cancer patients:

Total cases



- As of December 31, 2023, a total of 1,398 cases collected
- Depending on the treatment technology, each patient undergoes approximately 220-480 days of postoperative follow-up tracking

Cancer



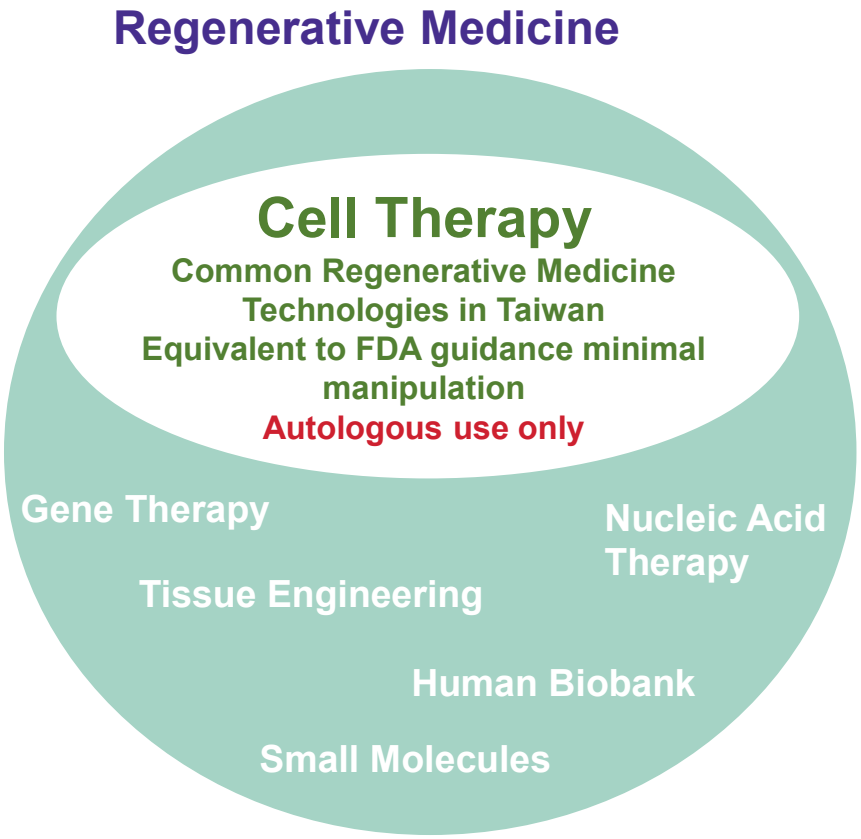
- As of December 31, 2023, a total of 911 cases have been enrolled to analyze the effects of cell therapy. (227 of 1138 cancer patients have signed the consent but never showed up then.)
- Regular follow-up of patients completing autologous immunocyte therapy indicates that they can survive on average nearly one year longer post-treatment

Dual-Track Management Model for Cell Therapy: Technologies and Products

	Technology	Product
Competent authority	Department of Medical Affairs, MOHW	Taiwan Food and Drug Administration, MOHW
Responsible unit	Medical institution	Pharmaceutical companies
Development Goals	Cell therapy technologies	Cell therapy products, gene therapy products, tissue engineering products, combination products
Control	• GTP: Good Tissue Practice for Human Cells and Tissues • Approved 6 items: immunocytes, adipose-derived stem cells, fibroblasts, mesenchymal stem cells, chondrocytes, hematopoietic stem cells	• GTP, GMP (Good Manufacturing Practice) • Obtain required licenses for sale

Taiwan Cell Therapy Management Model: Technology

Taiwan Cell Therapy Management Scope and Definition



Current Management Framework: Regulated under the " Regulation Governing the Application of Specific Medical Examination Technique and Medical Device (RASMET)"

The Regulation Governing the Application of Specific Medical Examination Technique and Medical Device (RASMET)

1. Items and Indications

- 6 low-risk cell therapy technologies
- Autologous use, predictable safety and efficacy

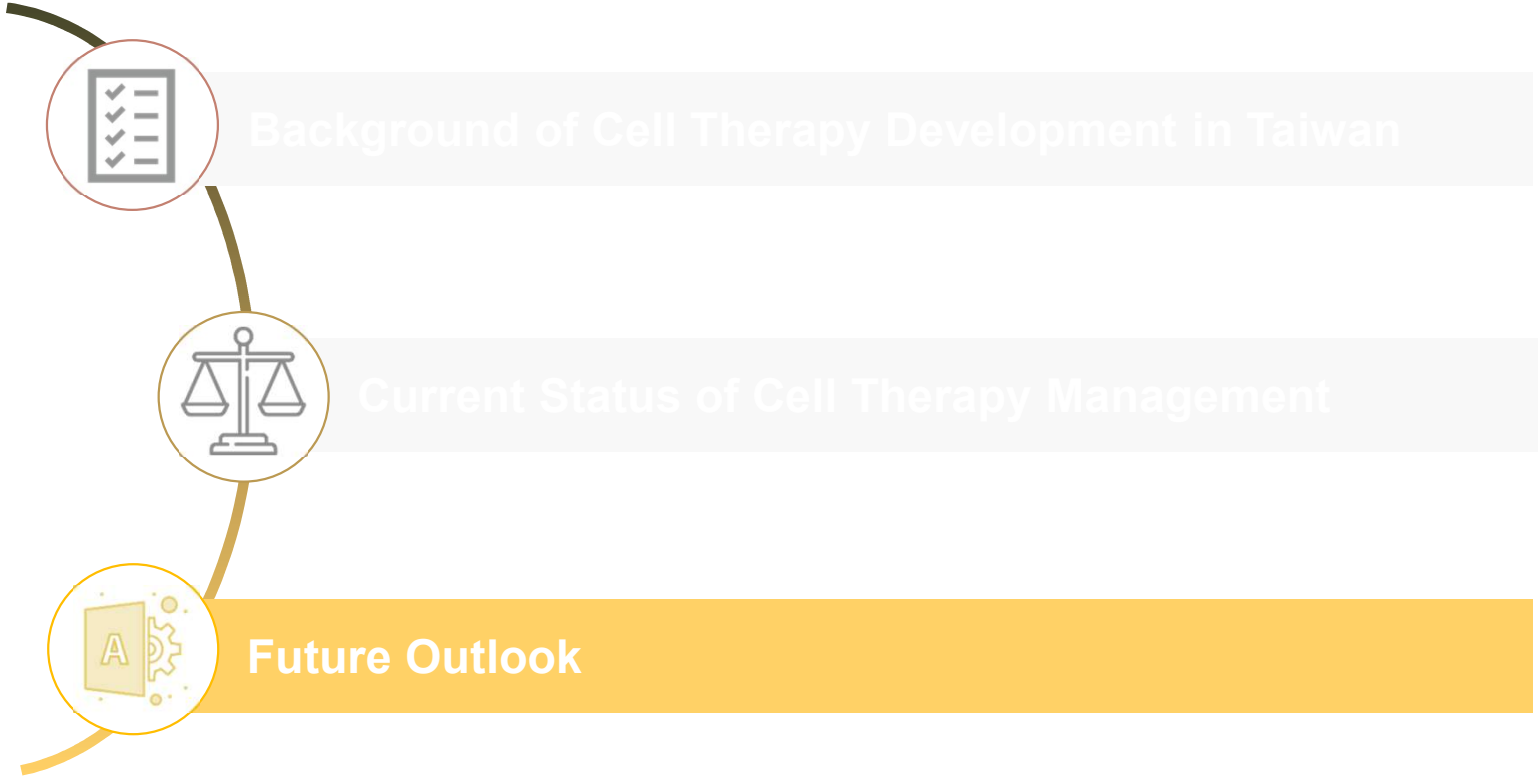
2. Permit System (up to 3 Years)

- Medical institutions must apply for approval from MOHW and register with the local health bureaus before proceeding
- Cell preparation facilities must be compliant with GTP regulations

3. Regular Reporting of Treatment Results

- Medical institutions must submit annual implementation reports
- If patient rights are affected or if there are abnormal numbers or severity of adverse events, implementation may be terminated

Outline


Background of Cell Therapy Development in Taiwan
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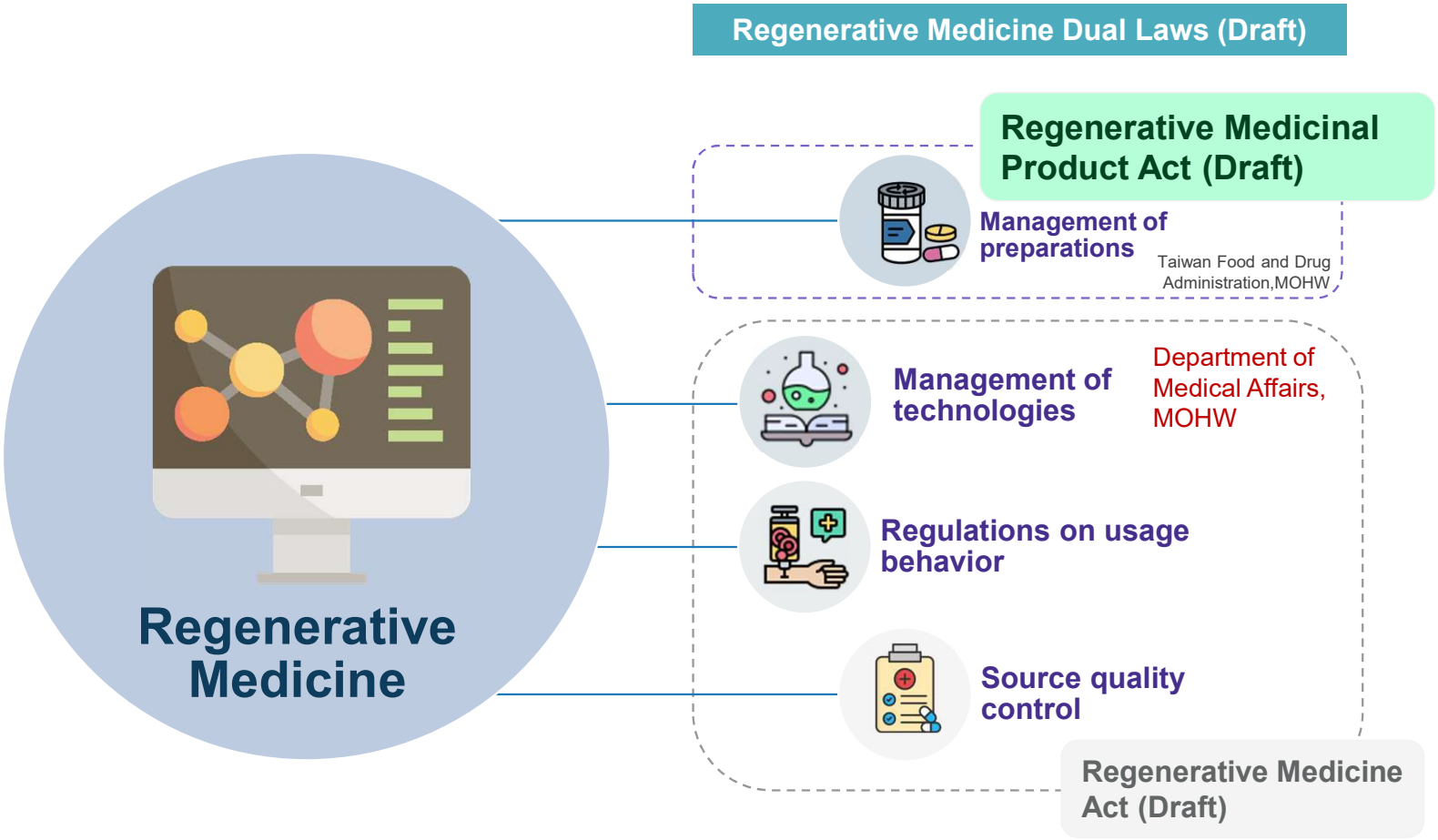
Future Outlook

Future: Implementing Quality Control through Graded and Triage Management



the Executive Yuan has approved two draft bills proposed by MOHW on April 24,2024.These bills are submitted to the Legislative Yuan for review now.

Promote the Core Value of Regenerative Medicine

1

Driven by policies to foster industrial technological innovation

Supporting Policy Environment and Investment by Private Sector

From the RASMET *to Dual Laws on Regenerative Medicine*, amendments are made to correspond to the appropriate legal hierarchy and keep pace with the times, ensuring a sound development environment for the industry and accelerating research and innovation.

Accelerating Technological Research and Innovation

2

Dual-track quality control for technologies and products

Qualified Physicians and Medical Institutions and Certified Pharmaceutical Companies

By specifying in regulations the qualifications required for physicians and medical institutions to perform cell therapy, as well as the certifications necessary for pharmaceutical companies engaged in product research and development, all activities are ensured safe and of high quality.

Ensuring Quality of Treatment and Research

3

Achieving information transparency through digital governance

Postoperative Follow-up of Patients and Regular Disclosure of Follow-Up Info

Through data governance and public information disclosure, information disparities within the industry are reduced, stimulating demand and improving management processes to promote the development of Taiwan's regenerative medicine ecosystem.

Stimulating Demand and Promoting Development

Objectives of Regenerative Medicine Policy

Enhancing Healthcare Quality

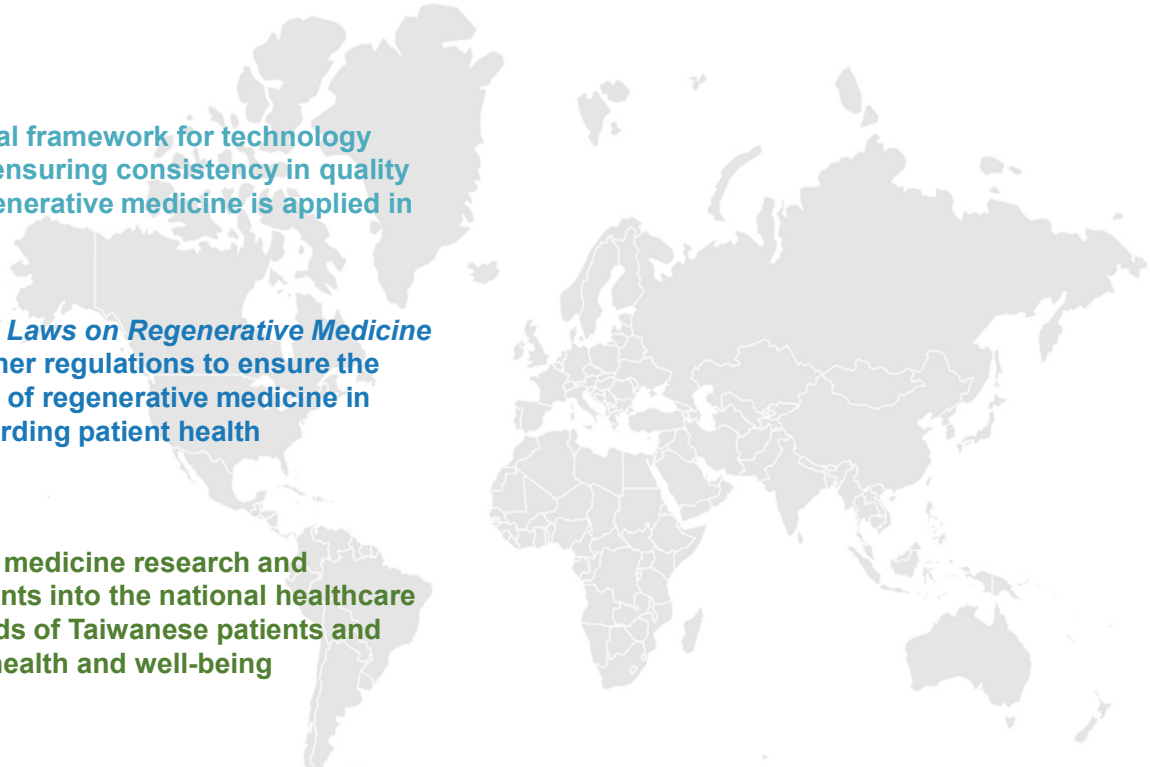
Through a dual-track legal framework for technology and product regulation, ensuring consistency in quality and standards when regenerative medicine is applied in clinical practice

Ensuring Patient Safety

Complementing the *Dual Laws on Regenerative Medicine* with the RASMET and other regulations to ensure the appropriate and safe use of regenerative medicine in clinical settings, safeguarding patient health

Promoting Availability and Accessibility

Incorporate regenerative medicine research and technological achievements into the national healthcare system, meeting the needs of Taiwanese patients and improving overall good health and well-being



Good Health and Well-being

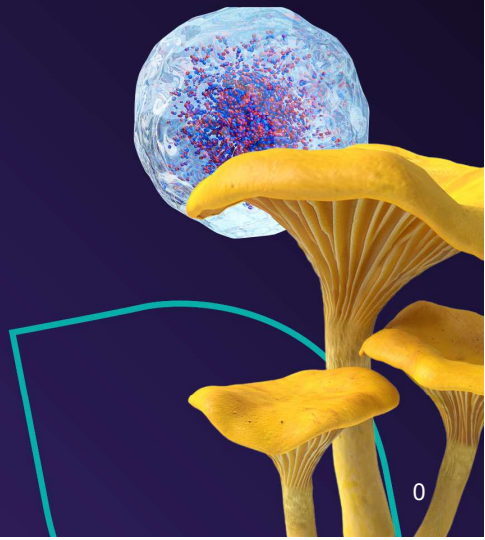
Success by design, not by chance!

Thank You For Your Attention!

Questions?
Comments?

Current Status on Cell/Gene Therapy Development in Japan

Yoshiaki Maruyama, Ph.D.
Director,
Office of Cellular and Tissue-based Products
PMDA, Japan



DISCLAIMER : The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA

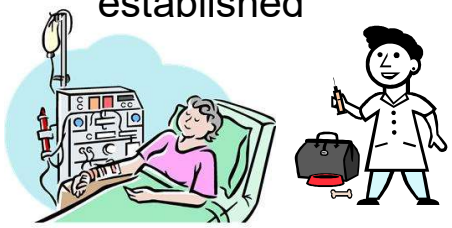
Dual Regulation of Regenerative Medicine in Japan

Technology & Product

Regenerative Medicine

Enacted on
25 November 2014

All medical **technologies** using processed cells which safety and efficacy have not yet been established



Production and marketing of regenerative and cellular therapeutic **products** by firms

Safety Act

The Act on the Safety of Regenerative Medicine

Medical Care / Clinical Research
Academic Research Purpose

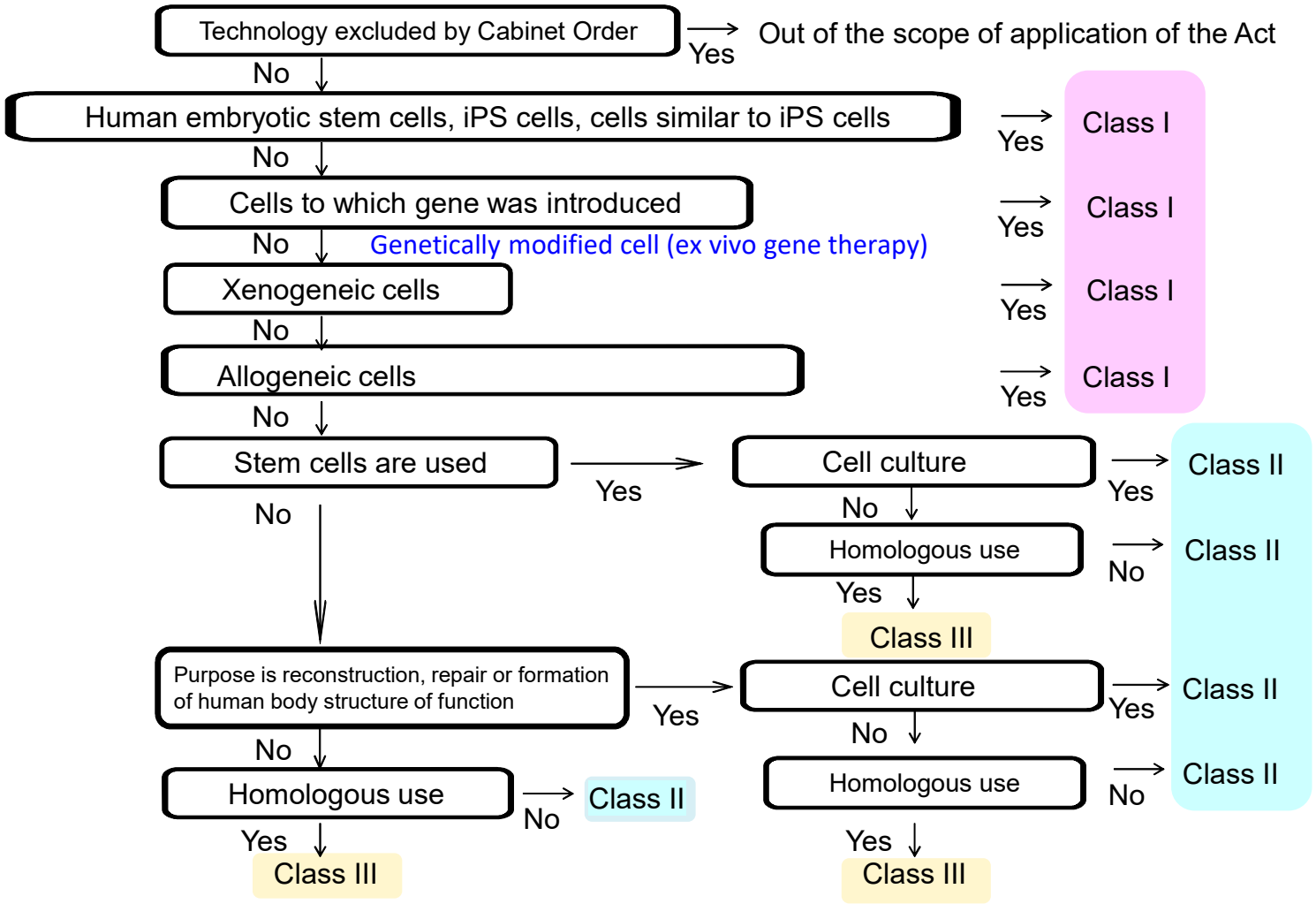
The Act on Pharmaceuticals and Medical Devices

PMD Act

Commercial Product
Marketing Authorization Purpose

Risk Classification Regenerative Medical Technology

Safety Act



Class	Medical Care	Clinical Research
I (High risk)	7	16
II (Middle risk)	1,571	43
III (Low risk)	3,898	42

(As of 1 December 2023)

Current Activity

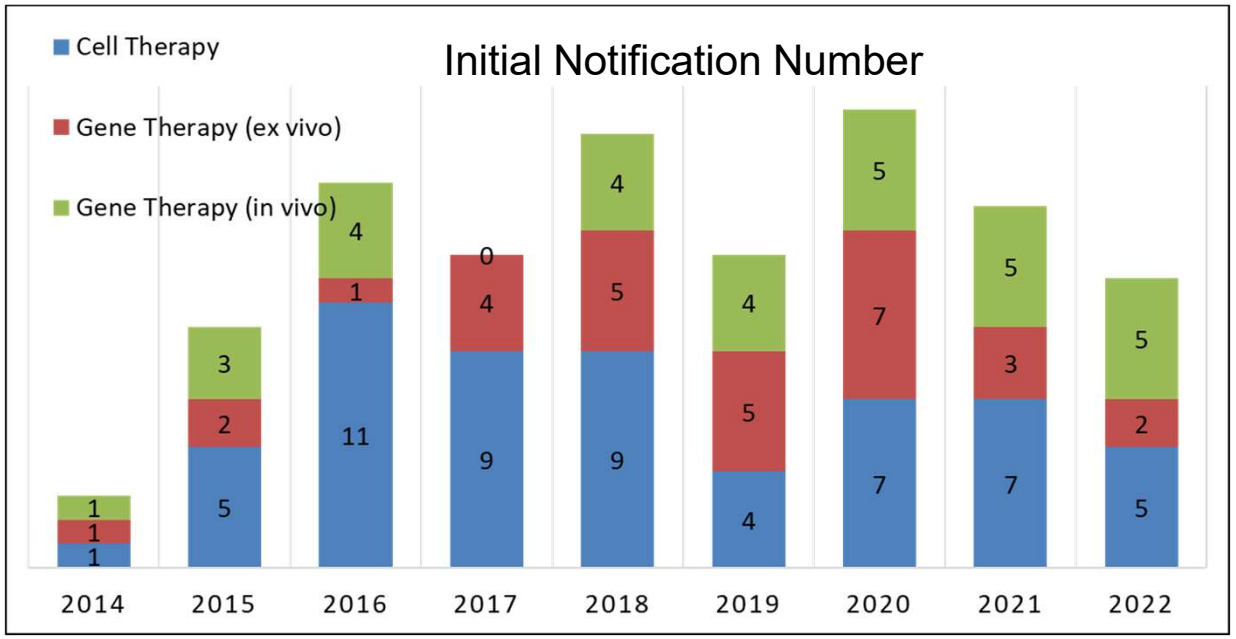
WG has been establish to review the Safety act, and studies are being conducted.
in vivo gene therapy is currently out of scope. *in vivo* gene therapy is also under consideration for inclusion in the scope of Safety act.

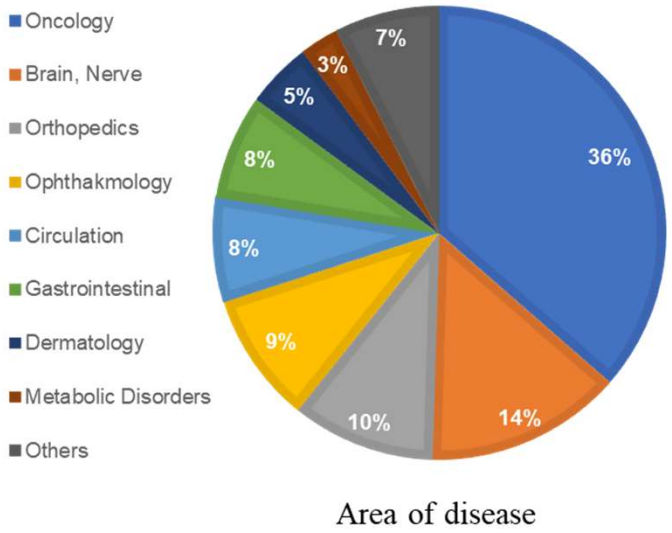
INDs Reviewed by PMDA

PMD Act

Notification	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
Initial	3 [1]	10 [2]	16 [7]	13 [8]	18 [8]	13 [7]	19 [9]	15 [7]	12 [3]	119 [51]
2nd or later	1 [1]	3 [2]	5 [0]	14 [10]	17 [3]	16 [7]	22 [5]	18 [9]	25 [14]	121 [51]

Note: The table in brackets in parentheses indicate the number of notifications of “investigator-initiated clinical trials (IIT).





Area of disease

Approved Products Reviewed by PMDA

4 somatic cell derived products

7 somatic stem cell derived products

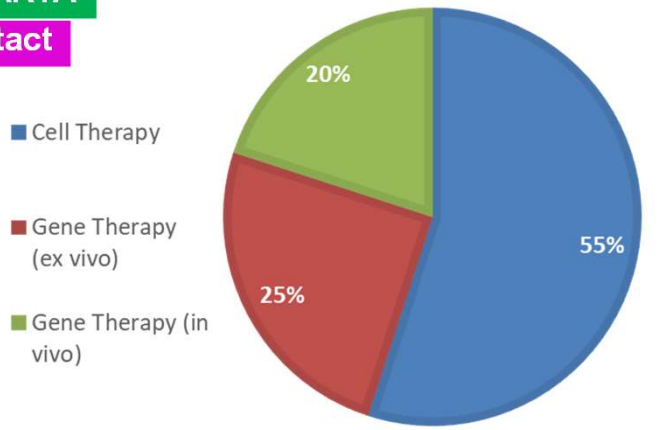
5 *ex vivo* gene therapy products

4 *in vivo* gene therapy products

20

PMD Act

LUXTURNA
JACEMIN
Vyznova
Sakracy
Abecma
CARVYKTI
Aloficel
Ocural
Breyanzi
YESCARTA
Delytact
Nepic
ZOLGENSMA
Kymriah
Collategene
STEMIRAC
TEMCELL HS
HeartSheet
JACC
JACE



(As of 1 Jun 2024)

2007 2012 2015 2018 2019 2020 2021 2022 2023

Summary of Approved Products in Japan

PMD Act

	Japan Origin (12)	Global (8)
Cell Therapy Products (16)		
Somatic cell derived products (9)	JACE (Skin) JACC (Knee) JACEMIN (Skin) Vyznova (Eye)	Kymriah YESCARTA Breyanzi Amecma CARVYKTI CAR-T
Somatic stem cell derived products (7)	HeartSheet* TEMCELL HS STEMIRAC * Nepic (Eye) Ocural (Eye) Sakracy (Eye)	Aloficel
iPS cell derived products (0)	---	---
Embryonic stem cell derived products (0)	---	---
Gene Therapy Products (4)		
Plasmid vector products (1)	Collategene*	---
Viral vector products (2)	---	ZOLGENSMA LUXTURNA AAV
Others (1)	Delytact *	

Area of disease
Oncology (6)
Ophthalmology (5)
Brain, Nerve (2)
Circulation (2)
Dermatology (2)
Others (3)

*Conditional and Time limited Approval

Ophthalmology Area

PMD Act

Epithelial cell sheet for limbal stem cell deficiency (LSCD), a rare and intractable corneal epithelial disease

https://www.jpte.co.jp/business/regenerative/

https://www.jpte.co.jp/business/regenerative/

http://hirosaki-li.co.jp/products_sakracy.html

Nepic
(Human (autologous) corneal limbus-derived corneal epithelial cell sheet)
(Mar 2020)

Ocural
(Human (autologous) oral mucosa-derived epithelial cell sheet)
(Jun 2021)

Sakracy
(Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate)
(Jan 2022)

Aketa et al., The Ocular Surface. 29, 220-225 (2023)

2020 | 2021 | 2022 | 2023

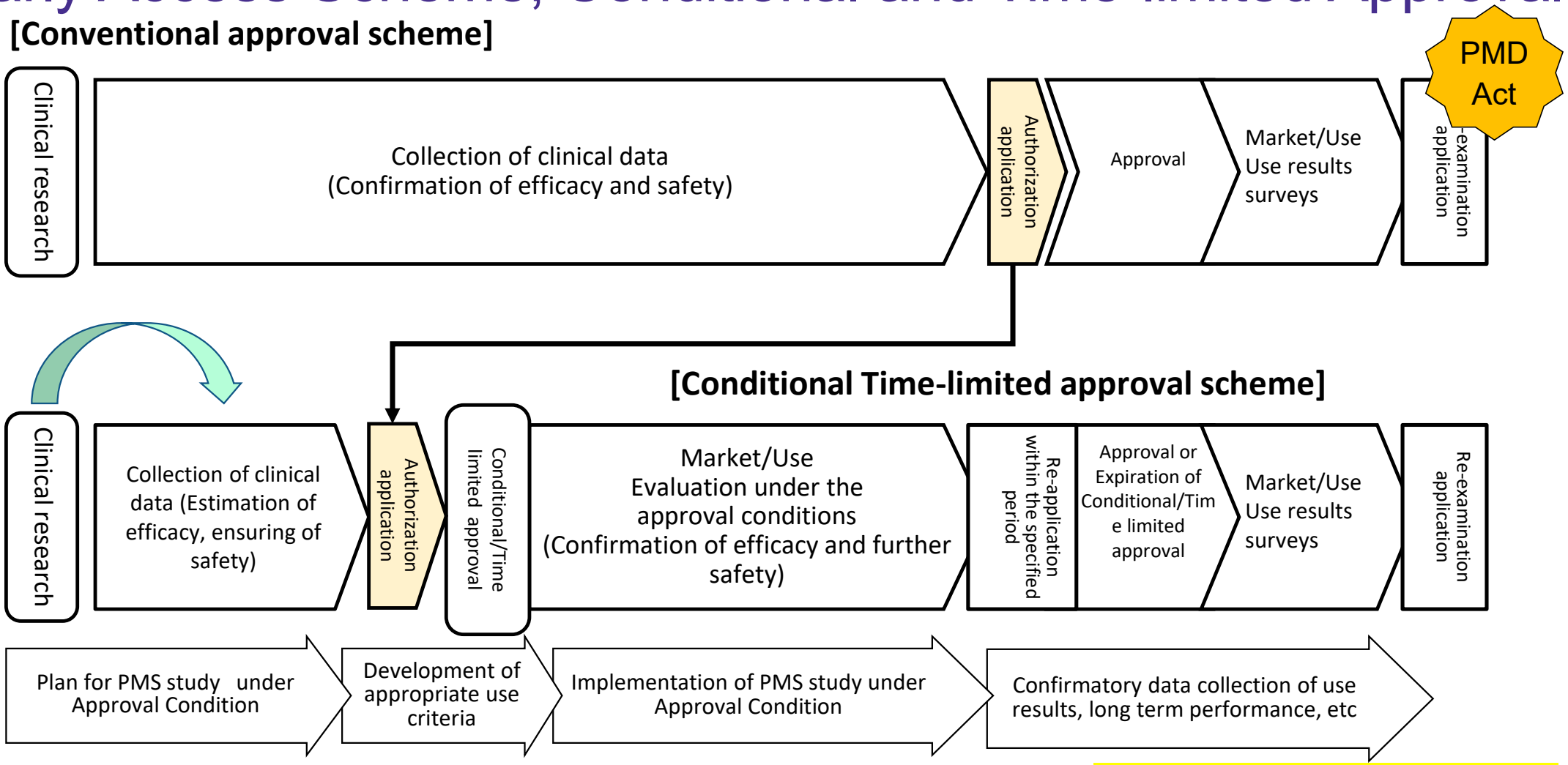
Vyznova
(Human (allogenic) corneal endothelium-derived endothelial cell injection)
(Mar 2023)

Endothelial cell injection for Bullous Keratopathy, a rare and intractable corneal endothelial disease

LUXTURNA
(voretigene neparvovec)
Confirmed biallelic RPE65 Mutation-associated retinal dystrophy
(Jun 2023)

Adeno-associated virus (AAV) vector

Early Access Scheme; Conditional and Time-limited Approval



Maruyama et al., Adv Exp Med Biol, 1430, 155-179 (2023)

Outline of the Condition for Approval and Granted Time-period for PMS Study

Products	HeartSheet	Stemirac	Collategene	Delytact
	Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard	Spinal cord injure	The treatment of ulcers in patients with chronic arterial occlusion	Malignant glioma
Granted time-period	8 years (17/09/2023) (Extend on 20/11/2018 after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council)	7 years (27/12/2025)	5 years (25/03/2024)	7 years (10/06/2028)
Efficacy evaluation				
Primary endpoint	Time to cardiac death (at ≥ 2 years post transplantation)	Cohort I; Patients with AIS Grade A at 6 to 8 weeks (49 ± 7 days) after injury Percentage of patients achieving ≥2 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury Cohort II; Patients with AIS Grade B or C at 6 to 8 weeks (49 ± 7 days) after injury Percentage of patients with AIS Grade B or C achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury	The proportion of patients with completely closed ulcer at 12 week later after injection	OS (from the day of diagnosis of malignant glioma to death [from any cause]): For each population of patients with primary glioblastoma and patients with recurrent glioblastoma, conduct a trend score matching so that the Delytact and control groups include the same number of patients (1:1), and perform a log-rank test with the two-sided significance level of 5% on OS in the sample population.
Number of subject				
Product	60	Cohort I; 27 Cohort II; 63	120	Glioblastoma: 250 Grade III malignant glioma: 60 to 100
Control (External)	120	Cohort I; 54 Cohort II; 125	80	Glioblastoma: 500 Grade III malignant glioma: 120 to 200

Summary

- 20 cell and gene therapy products, including 9 gene therapy products, have been approved under the PMD Act.
- 4 of 20 products have been approved through comprehensive framework for patient access (conditional and time-limited approval scheme). Sponsors are subject to strict post-marketing surveillance (PMS) study to prepare re-marketing authorization submission with in the granted time-period.
- Accelerated pathways are introduced in many countries. Regulators need to consider on how to collaborate for those development.

Information; PMDA Website

Regenerative Medical Products

1. Regulatory Framework

Regenerative medicine, which is expected to overcome intractable and serious diseases, is expected to play an important role in conventional medicine worldwide. The Japanese government must implement comprehensive policies to promote the development of regenerative medicine, inform the public, and increase public acceptance, and ensure that medical professionals and investigators cooperate with the policies. In this background, two regulatory frameworks for regenerative medicine, "The Act on the Safety of Regenerative Medicine " (ASRM) and the "Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act " (PMD Act), came into effect in November 2014. The ASRM sets out legal regulations not only for research, but also for the daily medical practice of cell therapy, which had previously been under the jurisdiction of the Medical Practitioners' Act and the Medical Care Act .

The PMD Act regulates the commercialization of regenerative medical products. Regenerative medical products in the PMD Act are defined as:

a. Processed (more than minimal manipulation) live human/animal cells that are intended to be used for either

- reconstruction, repair, or formation of structures or functions of the human body

Review Reports: Regenerative Medical Products

A

Brand Name	Non-proprietary Name	Approved In	English	Japanese
Abecma	idecabtagene vicleucel	January 2022		
Alofisel	darvadstrocel	September 2021		

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B

Brand Name	Non-proprietary Name	Approved In	English	Japanese
Breyanzi Initial Approval	lisocabtagene maraleucel	March 2021		
Breyanzi Partial Change Approval	lisocabtagene maraleucel	December 2022		

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Recent Publication

- Maruyama Y, Noda S, Okudaira S, Sakurai A, Okura N, Honda F. Regulatory Aspects of Cell and Gene Therapy Products: The Japanese Perspective, Adv Exp Med Biol, 1430, 155-179 (2023) https://doi.org/10.1007/978-3-031-34567-8_9
- Maruyama Y, Sakurai A, Noda S, Fujiwara Y, Okura N, Takagi T, Asano J, Honda F. Regulatory Issues: PMDA Review of Sakigake Designation Products: Oncolytic virus therapy with Delytact Injection (teserpaturev) for malignant glioma, The Oncologist, 28(8) 664-670 (2023) https://doi.org/10.1093/oncolo/oyad041
- Aketa N, Kasai M, Noda S, Asano J, Kunieda A, Kawanishi S, Maruyama Y, Honda F. Insights Into the Clinical Development of Regenerative Medical Products Through a Comparison of Three Cell-based Products Recently Approved for Limbal Stem Cell Deficiency. The Ocular Surface, 29, 220-225 (2023) https://doi.org/10.1016/j.jtos.2023.05.008
- Sakurai A, Kanzaki S, Honda F. Japanese pharmaceutical regulations of engineered viral vectors for medical use compared with those in the US and EU. Clinical Pharmacology & Therapeutics (2023) https://doi.org/10.1002/cpt.2788
- Fujiwara Y, Maruyama Y, Honda F. Balancing safety and efficacy with early availability in the regulation of regenerative medicine product. Clin Pharmacol Ther, 109:1182-1185 (2021). https://doi.org/10.1002/cpt.2034

WHERE BUSINESS & BREAKTHROUGHS **CONVERGE**

Thank you for your attention!

Please visit the PMDA website

Bio Events International Convention

June 3-6, 2024
San Diego, CA

Patients Wait Less-Streamlining Regulatory Pathways for Cell/Gene Therapies in Asia-Pacific Region:

Driving Success in CGTs Clinical Trials with Innovative Approaches

Chia-Hua Maggie Ho, D.Phil
Chief Operating Officer
Amarex Taiwan LLC
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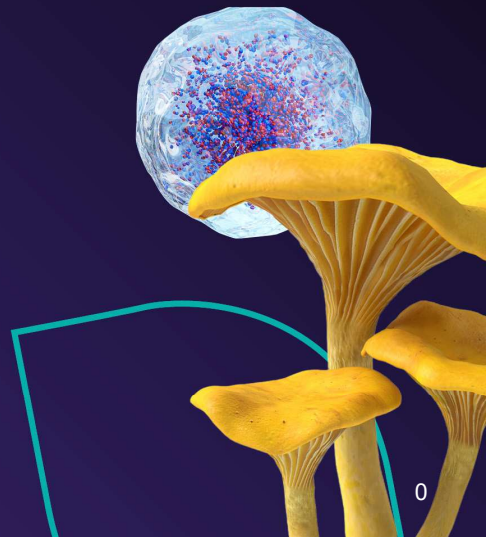
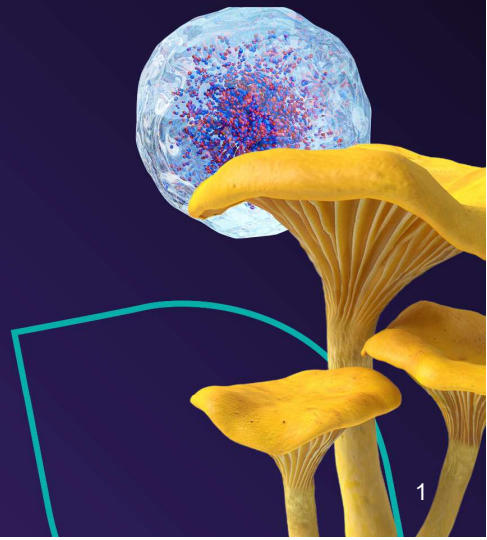
June 3, 2024



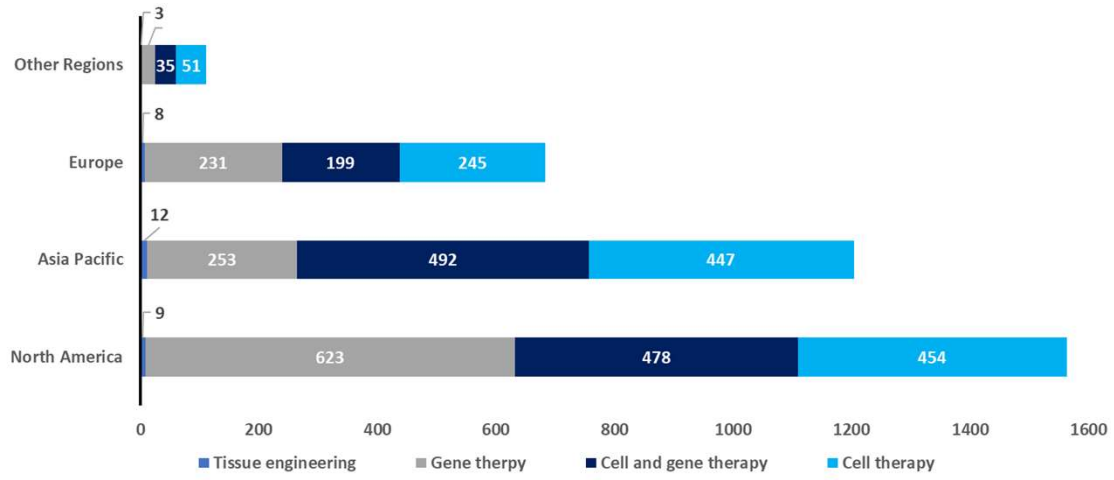
Outline

- Clinical Landscape of CGTs Development
- Clinical Risk of CGTs
- Successful Factors in CGTs Clinical Trial Design
- Innovative Clinical Trial Designs (ICTD) for CGTs
- The Way Forward for ICTDs
- Take Home Message



Clinical Landscape of CGTs Development

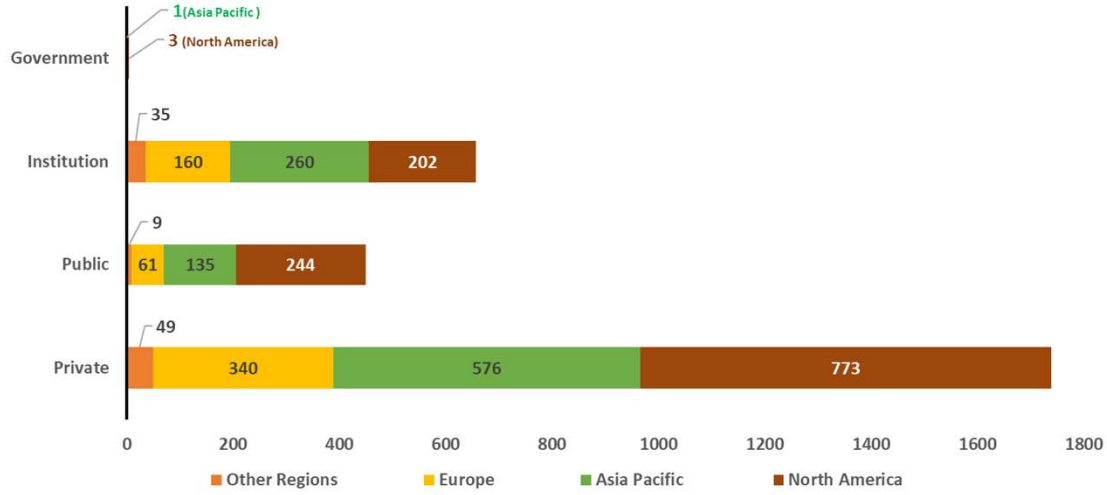
Developers by Headquarter Region and Therapeutic Approach (By April 2024)



Developers may work across multiple therapeutic approaches

	North America	Asia Pacific	Europe	Other Regions
Developers	1222	972	561	93
%	43	34	20	3

Developers by Entity Type and Headquarter Region (By April 2024)



	Government	Institution	Public	Private
Developers	4	657	449	1738
%	0.1	23	16	61

Resource: Alliance for Regenerative Medicine

Clinical Risks of CGTs

Risk of Gene Therapies

- Effects on the recipient genome
  - ✓ Alteration of expression of recipients' gene
  - ✓ Insertional oncogenesis
  - ✓ Germline change
- Direct effects of the transgene
  - ✓ Prolonged uncontrolled biological activity
  - ✓ Autoimmune-like reaction to self antigens
- Immune/host response to vector

Risk of Cell Therapies

- Cell differentiation to undesired cell types
- Ectopic tissue formation
- Uncontrolled tumorgenicity
- Cell migration to non-target site(s)
- Immunogenicity
- Graft-vs-host effects

Mitigating these risks for first-in-man clinical trials depends heavily on the data generated by preclinical animal studies.

Successful Factors in CGTs Clinical Trial Design

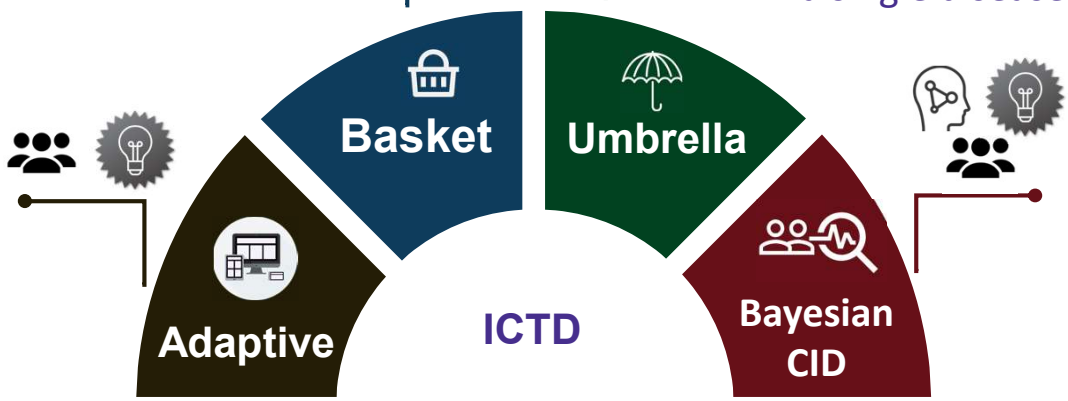
- Factors that impact the sample size and number of arms that can not be dealt with in a traditional trial design such as high response rate variability
- Use known prognostics factors stratification at the randomization stage or analyses of covariance at the analyses stage, or both approaches
- Establish well-designed, high-performing virtual patient registries to combat small patient populations and allow for longitudinal and post-authorization safety and efficacy studies

Innovative Clinical Trial Designs (ICTD) for CGTs

A master protocol designed to test a single investigational drug or drug combination in different populations

A master protocol designed to evaluate multiple investigational drugs administered as individual drugs or as drug combinations in a single disease population

Clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.



A clinical trial design that combines the use of prospective and retrospective data

Clinical Trial Design Challenges

Small sample size | Product novelty | Product complexity

CID: Complex Innovative trial Design

The Way Forward for ICTDs

Three things needs to be pay attention!

- The growing demand to digitize clinical trials
  - Enhance participant recruitment
  - Improve accuracy of data collection
  - Facilitate date analysis
- Differences in the level of guidance between countries
  - It is crucial to have a one-on-one consultation session to align with authorities on their expectations for regulatory approval filings.
- Relative novelty and risk of ICTDs
  - Although ICTDs have the potential to offer significant benefits for CGTs, developers must still perform thorough due diligence to assess whether this trial design approach is suitable for their investigate product

Take Home Message

- There is no “one size fits all” approach to CGTs and we have to be aware of this when designing and conducting CGTs studies. Others didn’t do it doesn’t mean you can not!!
- Traditional pre-clinical study may not provide all the necessary information for designing early phase studies. It's crucial to consider the product's specific characteristics and seek alternative approaches.
- Using ICDTs will be an excellent tool to deal with some of the limitations from CGTs.
- Engaging with regulatory authorities early in the product development process or finding a partner with extensive experience might be a good approach.

Amarex’s Experiences

20+	330+	64000+	130+	26
Years	Trials	Patients	IND/IDE	NDA/BLA/PMA/510K Approvals

Thanks for Your Attention!
Questions?

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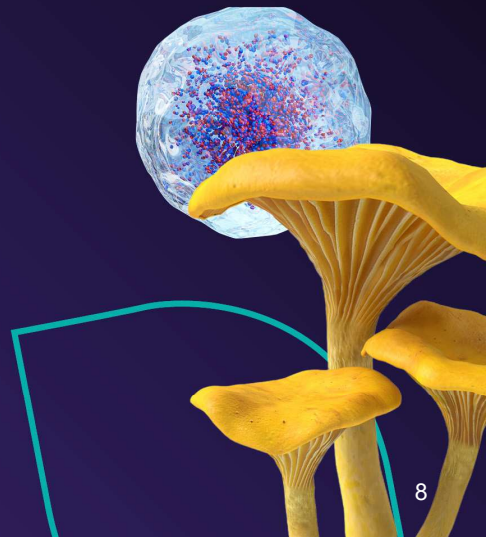


Please visit Amarex's Website:

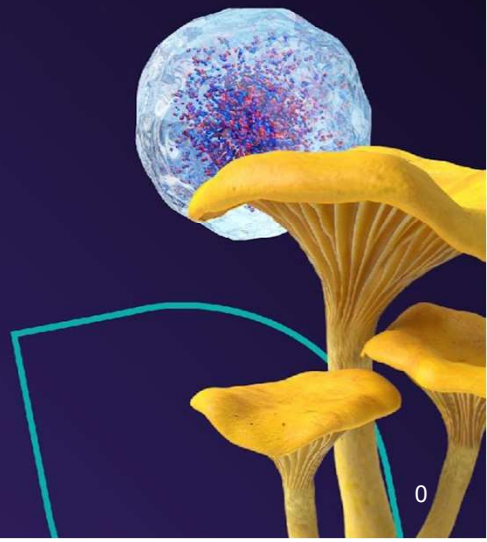
Cell and Gene Therapies: Global Outlook and Emerging Policy Issues

Joseph Damond

Chair, Global Life Sciences

C&M International LLC

BIO International Convention
June 3, 2024



Background

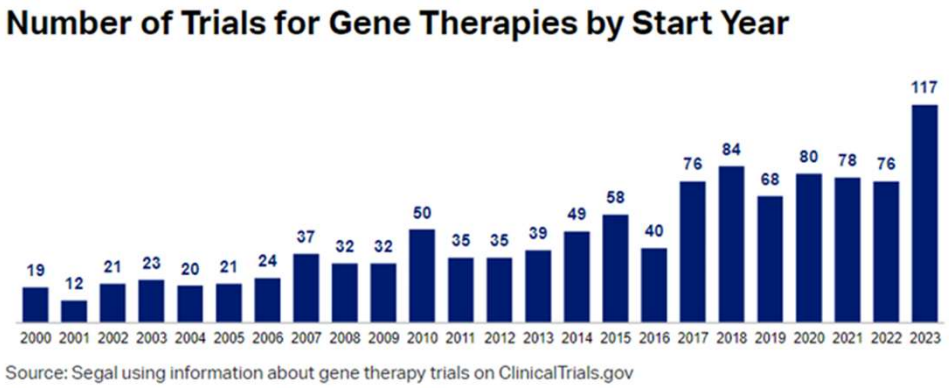
Cell and Gene Therapy: Transforming Healthcare

- Extraordinary advancements fueling CGT –
  - In genetic engineering, immunology and cellular biology
- Transformative therapies –
  - Realizing treatment for rare and difficult-to-treat diseases, cancers and disorders
  - Applying new treatment approaches to existing methodologies
- Precision medicine –
  - Tailoring treatments for patients based on their specific genes or other unique characteristics

CGT Development Over Time

Significant growth in the CGT sector, marked by increases in clinical trial activity, venture funding, geographic expansion, and regulatory approvals

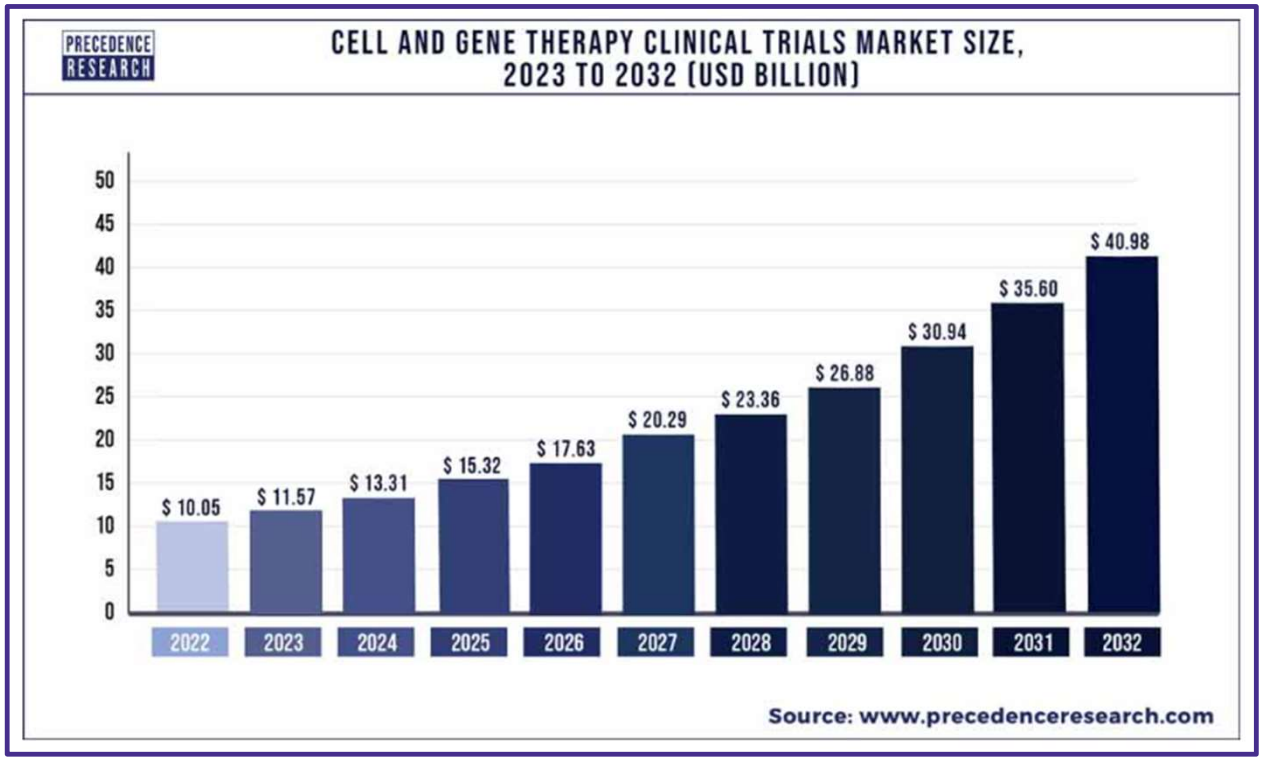
- **3,285 CGT trials** initiated in the past 5 years, with 631 starting in 2023
- CGT clinical trials have seen a global **annual increase of 20-25%** since 2010
- Industry-sponsored CGT trials **more than tripled** in the last decade
- **76 CGTs** launched globally by 2023, **over double** the number in 2013



Source: Institute for Human Data Science

Global Clinical Trial Market Value

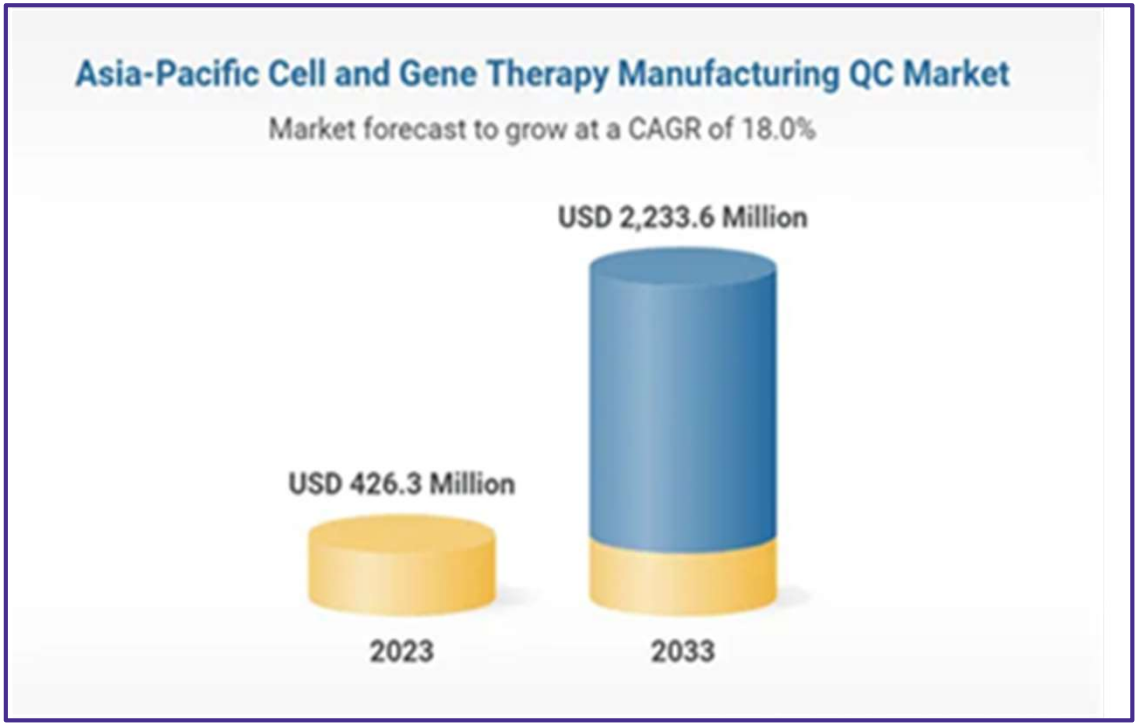
- The global CGT clinical trials market was assessed at US **$11.57 billion in 2023** and is expected **to increase to US $40.98 billion by 2032**, growing at a projected compound annual growth rate (CAGR) of **15.09% from 2023 to 2032**.



Source: Biospace

Market Growth – Geographic Distribution

- In 2023, **North America** leads with **48.3%** revenue share
- **Asia Pacific** second at **21.1%**
- APAC expected to **grow at 18% CAGR**, reaching $2,233.6M by 2033
- China's industry-sponsored trials **increased from 14% to 42%** in a decade



Source: Biospace; Research and Market Reports; Institute for Human Data Science

The CGT Pipeline

CGT Sector Data Q4 2023

- Currently a total of **1,920 clinical trials** encompassing Phase I through Phase IIII (Q4 2023)
- According to the Alliance for Regenerative Medicine, 2024 is expected to be the "**year of cell therapy"** predicting 17 CGT approvals in 2024

Cell And Gene Therapy Sector Data Q4 2023

GlobalData is ARM's data partner.

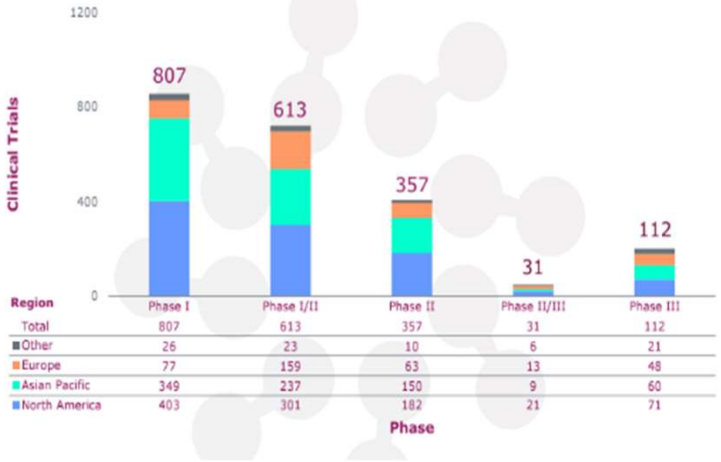
2023	North America	Asia Pacific	Europe	Total
Developers (Snapshot Value)	1,184	925	568	2,762*
Clinical Trials (Snapshot Value)	978	805	360	1,920*
Investment (Aggregate Value)	$8.3B	$2.1B	$1.2B	$11.7B*

Source: Alliance for Regenerative Medicine

CGT Trials by Phase, Region, and Sponsor

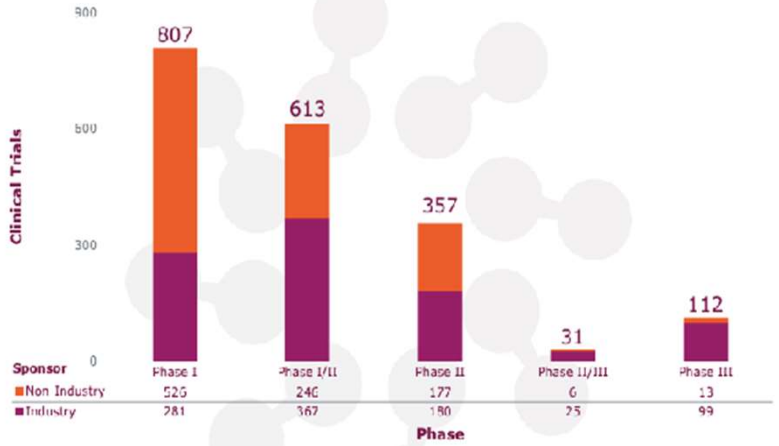
Ongoing Clinical Trials by Phase and Region

Alliance for Regenerative Medicine



Ongoing Clinical Trials by Phase and Sponsor

Alliance for Regenerative Medicine



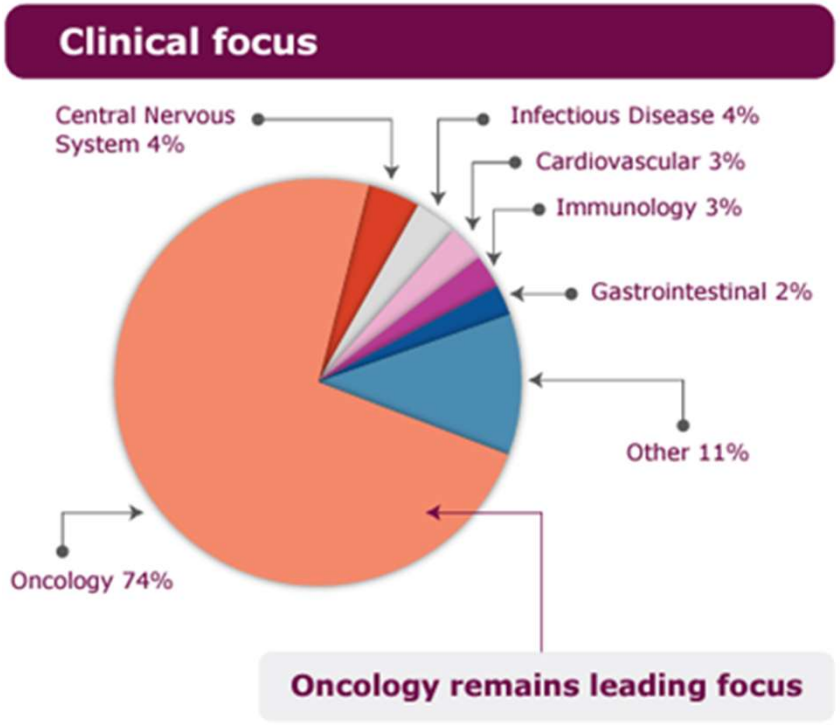
Source: Alliance for Regenerative Medicine

Current Clinical Focus

Three notable trends:

1. Enhanced efficacy in blood cancer treatment
2. Advancements in solid tumor treatment
3. Clinical breakdown in treating autoimmune disorders

- However, oncology continues to be the primary focus within the current clinical trial landscape



Source: Alliance for Regenerative Medicine

Policy Issues

Ethical Considerations

Adverse Outcomes / Risks –

- Unique and potentially irreversible risks, as well as unintended effects and risks associated with administration procedures. *May only emerge over time.*

Genetic Modification –

- GCT involving germline modifications raise ethical considerations regarding consent, potential unintended consequences, and the alteration of human genetics

Equity –

- Ensuring equitable access to these therapies across different populations and socioeconomic groups

Access and Affordability

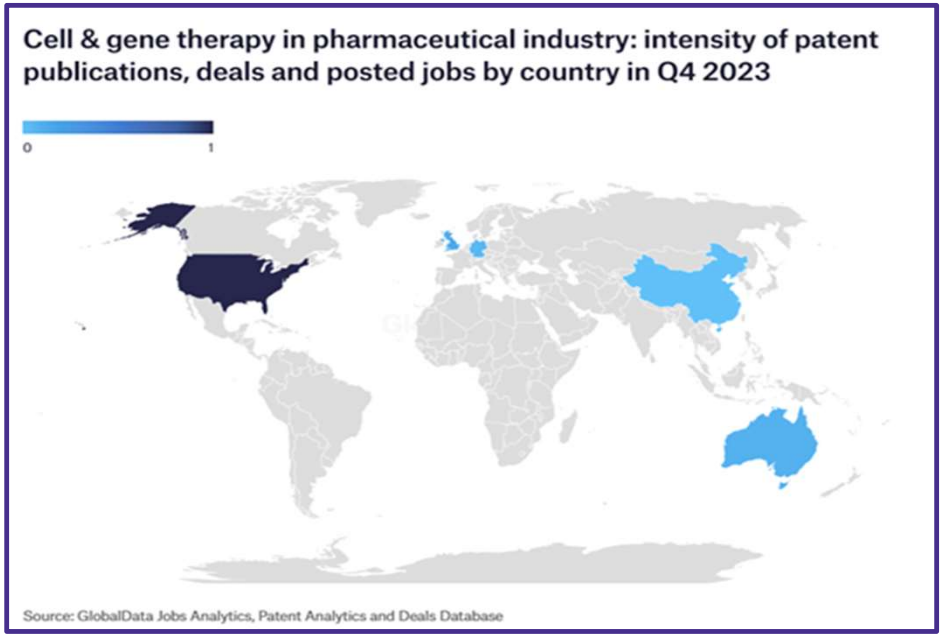
The **costs associated with CGT therapy may prove challenging** for payeors and patients seeking treatment.

- Pre- and post-treatment costs can include diagnostic tests, provider visitors, travel, and follow up-monitoring
  - Oncologic gene therapies: $65,000 – $475,000
  - Nononcologic gene therapies: $630,000 – $3.5 million
  - Hemgenix: $3.5 million / one-time intravenous infusion
  - Lantidra: $300,000 per patient
  - Vyjuvek: $15–$22 million / patient over their lifetime
- **Need for new financing solutions**: Long-term strategies for cost management – outcomes-based contracts, annuities, risk pooling, reinsurance gene-specific programs, etc. **Time to develop them is now.**

Intellectual Property and Innovation

IP protection for CGT presents new issues:

- Complex nature of biological materials and process involved. Difficult to define.
- Distinguishing between patentable inventions and natural phenomena
- Rapid scientific evolution and unique ethical considerations in genetic manipulation
- Difficulty in establishing clear, enforceable IP rights – but also challenges in “genericizing.”



Navigating the IP landscape for gene and cell therapies requires a comprehensive strategy that addresses patent protection, trade secrets, regulatory considerations, freedom to operate, and the ethical management of IP protections.

Infrastructure and Logistics

- As the CGT sector gains momentum globally, many countries are finding their **healthcare infrastructure cannot keep pace** with the rapid advancements and growing demand in CGT development and application
- Significant infrastructure and supply chain considerations include:
  - **Specialized manufacturing facilities**, stringent cold chain logistics, and limited treatment centers
  - These complicate scalability, increase costs, and limit patient access within and between countries

Regulatory Challenges

- Stem from their novel and complex nature, **requiring regulatory bodies to adapt and develop new frameworks** to ensure safety, efficacy and quality
  - Will **eventually** raise the issue how to regulate of **non-originator imitators**
- Includes navigating mostly uncharted territories in:
  - product approval processes
  - establishing standards for manufacturing and quality control
  - addressing ethical considerations, particularly with gene editing technologies.
- These challenges **demand ongoing collaboration** between innovators and regulators to facilitate the safe and effective integration of these therapies into clinical practice.
  - Also raises **issues of global norms and harmonization**

Thank You

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