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細胞與基因治療的技術發展與支付體系探討

A Study on the Technology Development and Payment System of Cell and Gene Therapy

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A Study on the Technology Development and Payment System of Cell and Gene Therapy

本論文係___劉昱玘___（P12E43001）在國立臺灣大學___生物科技管理碩士在職學位學程___，於民國 114 年 7 月 16 日承下列考試委員審查通過及口試及格，特此證明。

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中文摘要

細胞與基因治療（CGT）作為當代醫療創新的關鍵技術，具備根治罕見疾病與重大疾病的潛力。然而，其研發與商業化過程仍受到臨床不確定性、法規審查與支付機制限制的挑戰。本研究採用混合研究方法，結合專利分析、臨床試驗數據、國際制度比較與專家訪談，選取腺相關病毒（AAV）、嵌合抗原受體 T 細胞（CAR-T）、常間回文重複序列叢集關聯蛋白（CRISPR）、間質幹細胞（MSC）、自然殺手細胞（NK cell）與誘導性多能幹細胞（iPSC）等六種代表性技術，建構細胞基因療法的發展分類與成熟度評估架構。

透過美國、歐盟與日本的制度比較，本研究揭示不同法規與支付設計在 CGT 產品核准的偏好及產業發展的影響。最後特別聚焦於台灣現行雙軌制制度，並提出兼顧產業誘因與發展之建議。研究認為，影響 CGT 普及的關鍵並非僅止於技術發展，更取決於法規彈性、支付體系成熟度與整體政策前瞻性。

關鍵字：
細胞與基因治療、再生醫療、支付制度、法規體系、專利分析、台灣

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ABSTRACT

Cell and gene therapies (CGTs) represent a new frontier in biomedical innovation, offering curative potential for diseases once considered intractable. However, the development and delivery of CGTs remain constrained by uncertainties in regulation, reimbursement, and clinical translation. This study establishes an integrated analytical framework combining patent analysis, clinical trial mapping, and international policy comparison to examine six representative CGT modalities: AAV, CAR-T, CRISPR, MSC, NK cell, and iPSC. The analysis reveals differentiated technology trajectories and clinical maturity levels, which are used to develop a strategic group typology of CGT development. A cross-jurisdictional comparison of the United States, the European Union, and Japan further uncovers the heterogeneous structures of approval pathways and payment mechanisms.

Particular attention is paid to Taiwan's dual-track regulatory system and its implications for local innovation. The study proposes strategic recommendations for Taiwan's CGT governance, including regulatory alignment, HTA reform, data stewardship, and global standard integration of delivery capabilities. The findings suggest that beyond technology, institutional readiness and policy foresight are decisive in shaping the future of CGT accessibility and affordability.

Keywords: cell and gene therapy, regenerative medicine, payment system, regulatory system, patent analysis, Taiwan

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Chapter 1 Introduction

1.1 Research Background and Motivation

In April 2012, 12-year-old Emily Whitehead was enrolled in the clinical trial for her acute lymphoblastic leukemia (ALL) to receive CAR T-cell therapy, which she was diagnosed with in 2010, when she was 10 (Emily Whitehead Foundation, n.d.). Ten years later, Emily happily celebrated her cancer-free life since she received the treatment, showing the world the possibility of a long-term cure with one treatment (Children's Hospital of Philadelphia, 2022).

Cell and Gene Therapy (CGT), also known as Gene and Cell Therapy (GCT) or Cellular and Gene Therapy, has been one of the most discussed breakthroughs in biotechnology in recent years. It is broadly defined as the use of genetic material or cellular modification for therapeutic purposes, which has rapidly progressed from experimental approaches to front-line treatment in select indications.

The first approved human gene therapy in the Western world was Glybera in 2012 (Watanabe et al., 2015). Since then, a wave of CGT developments has emerged, targeting various diseases. By 2017, the FDA’s approval of Luxturna, Kymriah, and Yescarta marked a pivotal turning point in the development of CGTs (Pategou, 2025).

By the end of Q4 of 2024, 33 gene therapies and 72 cell therapies have been approved for clinical use globally; 2,117 gene therapies and 944 cell therapies are in development pipelines. Among them, oncology and rare diseases outnumbered other indications, and chimeric antigen receptor T cell (CAR-T) remains the most popular CGT (American Society of Gene and Cell Therapy & CITELINE, n.d.).

According to market research updated in February 2025, the market size of CGT reached $21.3 billion in 2024 and is expected to grow strongly at a CAGR of 18.7% from 2025 to 2034 (Precedence Research, n.d.).

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While the strong market potential of CGTs serves as a significant incentive for manufacturers to continue investing in the field, growing concerns have begun to surface that the current system may not be ready to embrace the challenges brought by CGTs. Among the concerns and discussions, one of the fundamental questions on the rise is whether the market can truly afford CGT, and if so, for how long it can sustain these costs.

Wong et al. (2023) conducted a simulation to estimate the projected number of patients receiving gene therapy per year, along with the corresponding annual costs in the United States, both in total and segmented by payer type. The simulation results indicate that, under conservative assumptions, annual spending on gene therapies is projected to reach approximately $20.4 billion, peaking at $25.3 billion in 2026 (Wong et al., 2023). Thus, while the CGT market is expected to expand rapidly, concerns remain about whether payers can afford the financial demands of these promising yet expensive therapies—a challenge that may ultimately determine whether the potential of CGTs can be fully realized or remain an unattainable ideal.

In 2017, uniQure announced that it would stop the renewal of Glybera in Europe (Warner, 2017). In 2021, Bluebird withdrew Zynteglo from Germany and shut down the operations of Skysona in Europe (Pagliarulo, 2021). The strategy of shifting the market focus from Europe to the US highlighted the difficulties for a new CGT product to be correctly valued.

In February 2025, Pfizer announced termination of further development and commercialization of their gene therapy drug “Beqvez”, a drug targeting hemophilia B. “Beqvez” gained US FDA approval in 2024 with a listed price of 3.5 million US dollars, but within a year of launch, the low market demand drove Pfizer to terminate Beqvez, an indication that the market was not ready for it (Pagliarulo, 2025).

Despite the government's efforts to support CGT commercialization through

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diverging payments by regulating insurance companies to cover CGTs within medical plans, there remains a risk of refusal, particularly for patients relying on self-insured organizations (Smith, 2024).

These cases highlight the limitations of CGT in the current system, and they are starting to worsen. This underscores the importance of an evaluation system for policymakers to consider, as it may be time for them to take more significant steps to accommodate the changes for the upcoming era of CGTs.

On the other hand, the development of the CGT industry in Taiwan is still in its early stages. The first CGT-related regulation was the Regulation Governing the Application of Specific Medical Examination Technique and Medical Device (RASMET), announced in 2018. Although RASMET opened the door for CGT in Taiwan, the high price and numerous limitations (e.g., only medical facilities are allowed) are restraining the CGT industry in Taiwan from truly developing. In 2024, the Regenerative Medicine Act and the Regenerative Medicinal Products Act were passed, marking a new milestone in Taiwan's development of CGT.

While industrial forums have been held to discuss future directions and payment challenges of CGTs (Peng, 2024), academic research on this issue remains limited, with no comprehensive studies conducted to date. Currently, most CGTs in Taiwan are performed as medical practices rather than standardized, commercialized products. Since only a few CGT products have been incorporated into the National Health Insurance (NHI) coverage, the immediate financial impact on the government's payment system has not yet become a critical issue. However, as the global CGT landscape continues to progress rapidly, Taiwan will soon face the same fiscal and systemic pressures that other countries are already experiencing.

From the experience gained from global developments in CGT, it is evident that

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CGT is not merely a scientific breakthrough, but a system-level innovation that requires the coordination of technological capabilities, clinical validation, regulatory mechanisms, and financial sustainability. In particular, the transition from research to reimbursement remains fragmented and uneven across jurisdictions. Taiwan, situated at the intersection of emerging legal frameworks and growing industrial interests, offers a unique context for exploring how a health system in transition can strategically engage with CGT under global pressure and local constraints.

1.2 Research Objectives and Questions

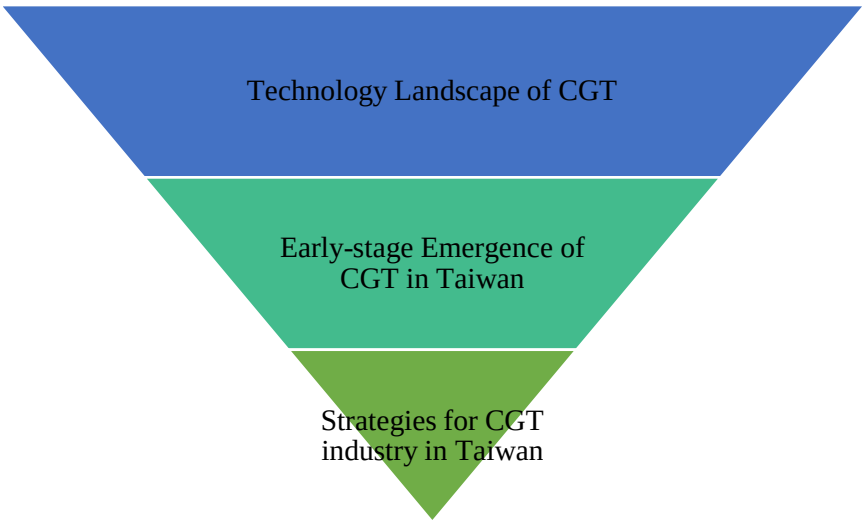

Figure 1-1

From Global Cell and Gene Therapy Expansion to Taiwan's Industrial Strategic

Note. Compiled by the researcher.

To clarify the logic behind the research focus, **Figure 1-1** presents an inverted pyramid showing the analytical narrowing from global CGT development to Taiwan's industrial strategies. Beginning with the global momentum behind CGT technologies, this study turns to Taiwan's early-stage efforts in CGT development. Ultimately, the central aim is to explore how Taiwan can strategically advance its CGT industry.

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Meanwhile, the biotechnology and pharmaceutical industry is often regarded as Taiwan's next strategic pillar, receiving strong policy attention and support. Since 2021, the contract development and manufacturing organization (CDMO) sector has drawn increasing interest and anticipation, particularly following amendments to the Act for the Development of Biotech and New Pharmaceutical Industry (Zhou & Lin, 2022). To identify high-potential areas and strengthen Taiwan's position in the global market, a careful and adaptive approach to system design and policy implementation is required.

Thus, the challenges that accompany CGT development, particularly those related to affordability, evidence generation, and institutional coordination, cannot be addressed solely by technical progress. This study thus examines how technological maturity, institutional readiness, and strategic policy instruments interact to shape the commercialization of different CGT modalities. The following research questions are formulated to reflect this interdisciplinary perspective:

1. What is the current state of development of primary CGT technologies?
2. What are the key limitations in commercializing CGT, particularly in terms of payment models and system readiness?
3. How can Taiwan plan for the future development of CGTs in light of these technological and systemic constraints?

Collectively, these three questions reflect a dual focus: (i) establishing an evaluative framework for the CGT industry, and (ii) integrating policy analysis with technology foresight, to inform both institutional reform and industrial preparation.

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Chapter 2 Literature Review

2.1 Technologies of CGT

2.1.1 The Definition of CGT

The US Food and Drug Administration (FDA) defines CGT as the integration of cellular therapy and human gene therapy. Cellular therapy products encompass a range of modalities, including cellular immunotherapies, cancer vaccines, and both autologous and allogeneic cells used for targeted therapeutic purposes. Examples of these cells include hematopoietic stem cells, as well as adult and embryonic stem cells. Human gene therapy refers to interventions that modify or regulate gene expression or alter the biological properties of living cells for therapeutic use. (US FDA, 2023a).

In Europe, gene and cell therapies are regulated under the framework of Advanced Therapy Medicinal Products (ATMPs). This classification ensures that such therapies meet rigorous standards of quality, safety, and efficacy before they are authorized for use (Sandra Johannesson, 2024).

ATMPs are classified into the following categories by the European Medicines Agency (EMA):

1. Gene Therapy Medicinal Products (GTMPs): include the insertion of recombinant genes into the body to treat diseases by regulating, repairing, replacing, adding, or deleting genetic sequences.
2. Somatic Cell Therapy Medicinal Products (sCTMPs): consist of cells or tissues that have been substantially manipulated to alter their biological characteristics or are intended for a different essential function in the recipient than in the donor. Used to treat, prevent, or diagnose diseases through the pharmacological, immunological, or metabolic action of the modified cells or tissues.

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3. Tissue-Engineered Products (TEPs): contain cells or tissues that have been modified to regenerate, repair, or replace human tissue.
4. Combined ATMPs: ATMPs that incorporate one or more medical devices as an essential part of the product, such as cells embedded in a biodegradable matrix or scaffold (EMA, n.d.).

In some academic definitions, CGT is further defined as a combination of gene, cell, and RNA therapies, as illustrated in **Figure 2-1**.

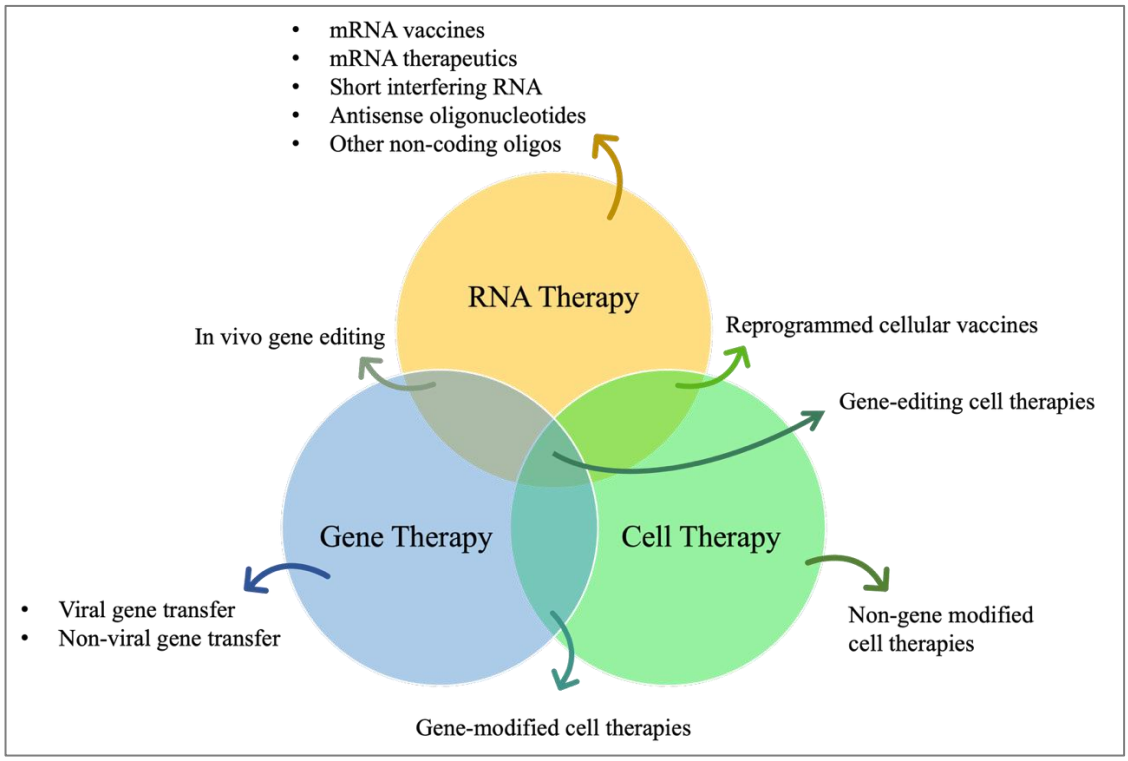

Figure 2-1

The Landscape of Cell and Gene Therapy

Note. Adapted from Chancellor et al. (2023) by the researcher.

To facilitate subsequent analysis, this study adopts a simplified classification scheme similar to that of the US FDA, categorizing CGTs into two overarching groups: gene therapy and cell therapy. The categorizing standard is whether gene modifications are included in the therapy or not.

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According to the American Society of Gene and Cell Therapy (ASGCT), gene therapy is the use of genetic material to treat or prevent diseases. On the other hand, cell therapy refers to the transfer of intact, live cells into a patient to help lessen or cure a disease.

However, CAR-T is categorized as a gene therapy in this study due to its gene-edited nature, which may be different from common understandings.

2.1.2 Gene Therapy

There are two ways to categorize gene therapies. One is to see where the gene modifications happen. For *in vivo* gene therapy, bioengineered genetic materials are delivered directly into the patient's body, where the gene acts as the active pharmaceutical ingredient, for instance, treatments utilizing viral vectors. *Ex vivo* gene therapy, on the contrary, involves collecting the patient's cells, performing genetic modification in the laboratory, and subsequently reinfusing the modified cells. Here, the therapy is mediated by the genetically engineered cells themselves, as seen in approaches like CAR-T cell therapy. Another way to classify gene therapies is by the approach used to modify genes, including gene delivery, gene modification, and gene editing (Kou, 2025).

Three specific gene therapies are selected for discussion, listed in **Table 2-1**.

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Table 2-1

Classification of Gene Therapy Approaches and Corresponding Modalities in This Study

Gene Therapy Approaches	Modalities Selected in the Study
Gene Delivery	Adeno-Associated Virus (AAV)
Gene Modification	Chimeric Antigen Receptor T Cell (CAR-T)
Gene Editing	Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

Note. Compiled by the researcher.

Adeno-Associated Virus (AAV)

AAV is a small, non-enveloped, non-pathogenic parvovirus widely used as a gene delivery vector (Issa et al., 2023; Kang et al., 2023; Naso et al., 2017). Its genome comprises two essential genes, *rep* and *cap*, flanked by inverted terminal repeats (ITRs) that facilitate replication and packaging (Issa et al., 2023; Ling et al., 2023; Zhang et al., 2022). Engineered recombinant AAV (rAAV) vectors remove these viral genes and insert therapeutic DNA, enabling targeted gene delivery (Issa et al., 2023; Kang et al., 2023; Naso et al., 2017). AAV is favored for its ability to transduce a wide range of cell types and its favorable safety profile, making it a leading platform in *in vivo* gene therapy (Issa et al., 2023).

Advancements in AAV technology focus on improving vector performance and safety. Innovations include:

- Capsid Engineering: New AAV capsids are designed through rational design, directed evolution, and machine learning to enhance tissue targeting and evade immune detection (Nisanov et al., 2025).
- Cassette Optimization: Strategies such as self-complementary AAV

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(scAAV), promoter selection, and RNA regulatory elements enhance both expression efficiency and safety (Au et al., 2021; Kang et al., 2023).

- Manufacturing Improvements: Scalable production methods, including producer cell lines and insect cell systems, aim to reduce costs and enhance product consistency (Kang et al., 2023; Naso et al., 2017; Young, 2023).
- Immunogenicity Management: To address pre-existing immunity and immune responses, approaches such as patient screening, immunosuppression, capsid modification, and plasmapheresis are being explored (Bing et al., 2022; Kishimoto & Samulski, 2022; Nisanov et al., 2025).

AAV vectors have advanced into clinical use across diverse disease areas:

- Ophthalmology: Luxturna (AAV2) treats inherited retinal dystrophies (Weber, 2021; Young, 2023).
- Neurology: Zolgensma (AAV9) is used for spinal muscular atrophy; other central nervous system (CNS) conditions include Parkinson's, Huntington's, and Batten disease (Issa et al., 2023; Kang et al., 2023; Ling et al., 2023; Young, 2023).
- Hematology: Hemgenix and Roctavian (AAV5) are used to treat hemophilia B and A, respectively (Issa et al., 2023; Young, 2023).
- Neuromuscular and Lysosomal Disorders: AAV vectors deliver therapeutic genes for Duchenne muscular dystrophy, Fabry, and Pompe disease (Au et al., 2021; Issa et al., 2023; Naso et al., 2017).
- Cardiology: Experimental AAV-based therapies target heart failure (Issa et al., 2023).
- Liver and Respiratory Diseases: AAVs are being evaluated in Wilson's

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disease, cystic fibrosis, and other monogenic disorders (Issa et al., 2023).

- Cancer: Investigational uses include suicide gene therapy and anti-angiogenesis (Issa et al., 2023; Ling et al., 2023).

Due to their flexibility, AAV vectors are at the forefront of gene therapy, with growing clinical success and expanding therapeutic potential across multiple fields.

Chimeric Antigen Receptor (CAR) T-cell

CAR-T is a form of gene-modified cell therapy that reprograms T lymphocytes to recognize and eliminate diseased cells, particularly cancer cells (Awasthi et al., 2023; Makita et al., 2017). This is achieved by introducing synthetic receptors, known as chimeric antigen receptors (CARs), which combine the antigen-binding domain of antibodies with intracellular T-cell signaling elements (Kast et al., 2022; Makita et al., 2017; Wang et al., 2023). CAR-T cells function independently of major histocompatibility complex (MHC) recognition, allowing for broader tumor targeting (June et al., 2018; Makita et al., 2017; Ramos & Dotti, 2011; Wang et al., 2023).

T cells are typically collected from the patient (autologous), genetically engineered using viral vectors (e.g., lentivirus, retrovirus) or non-viral tools (e.g., CRISPR/Cas9), expanded *ex vivo*, and reinfused into the patient (Hartmann et al., 2017; Ramos & Dotti, 2011; Wang et al., 2023). When CAR-T cells recognize and bind to their target antigen, they become activated, undergo proliferation, and eliminate the target cells through cytolytic processes (Ramos & Dotti, 2011).

CAR-T technology has progressed through multiple generations. First-generation CARs included only the CD3ζ activation domain (Kast et al., 2022; Makita et al., 2017). Second-generation CARs incorporated co-stimulatory domains, such as CD28 or 4-1BB, thereby enhancing cell persistence and activity (June et al., 2018; Ramos & Dotti, 2011).

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Third- and fourth-generation CARs incorporate additional signaling elements or payloads (e.g., IL-12) to overcome tumor resistance (Kast et al., 2022; Wagner et al., 2022). Fifth-generation designs employ genome editing to produce allogeneic, universal CAR-T products (Kast et al., 2022).

CAR-T production involves leukapheresis, T-cell activation, gene modification, expansion, and infusion, a process taking 2–3 weeks (Makita et al., 2017). Emerging rapid manufacturing platforms (e.g., T-Charge) shorten this to under 2 days while preserving T-cell stemness (Dickinson et al., 2023). Automated systems, such as CliniMACS Prodigy, are being adopted to streamline production and reduce costs (Wang et al., 2023). Potency and safety testing are also being optimized (Dias et al., 2024).

Allogeneic "off-the-shelf" CAR-T therapies use donor T cells that have been modified to eliminate endogenous T-cell receptors (TCRs) and human leukocyte antigen (HLA) expression, reducing risks of graft-versus-host disease (GVHD) and rejection (Kast et al., 2022; Makita et al., 2017). While early trials show feasibility, durability of engraftment and immune clearance remain concerns.

CAR-T therapy is linked to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Management includes using IL-6 inhibitors (e.g., tocilizumab) and corticosteroids (Li et al., 2024; Wang & Han, 2018). Suicide genes (e.g., iCasp9) and early biomarker monitoring are being studied to improve safety (Hartmann et al., 2017; Wang et al., 2023).

Regarding clinical applications, CAR-Ts have demonstrated substantial efficacy in treating hematological malignancies (Dickinson et al., 2023; Hartmann et al., 2017; Ramos & Dotti, 2011). FDA-approved products (e.g., Kymriah, Yescarta) target B-cell antigens, such as CD19 or B-cell maturation antigen (BCMA), to treat conditions like B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL),

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and multiple myeloma (Li et al., 2024; Wang et al., 2023; Wang & Han, 2018).

Progress in solid tumors has been hindered by antigen heterogeneity and immune challenges. Investigational targets include HER2, mesothelin, and epidermal growth factor receptor variant III (EGFRvIII) (Hartmann et al., 2017; June et al., 2018; Kast et al., 2022).

CAR-Ts are also expanding into non-oncology indications. In autoimmune diseases, CD19-targeted CAR-T therapies have demonstrated promising effectiveness in conditions such as systemic lupus erythematosus (SLE) and multiple sclerosis (Li et al., 2024). Regulatory CAR-T cells (CAR-Tregs) are under development for antigen-specific immune modulation.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

CRISPR and CRISPR-associated (Cas) protein system, particularly CRISPR-Cas9, has revolutionized genome editing and holds significant promise for gene therapy (Chehelgerdi et al., 2024; Uddin et al., 2020). In 2020, Jennifer Doudna and Emmanuelle Charpentier received the Nobel Prize in Chemistry for their discovery of this remarkable tool (Ng, 2024; The Royal Swedish Academy of Sciences, 2020).

Originating from a natural adaptive immune system in prokaryotes, such as bacteria and archaea, CRISPR-Cas systems provide defense against invading foreign genetic elements, including bacteriophages and plasmids (Fellmann et al., 2017; Guo et al., 2022; Uddin et al., 2020). The most commonly used system, CRISPR-Cas9, consists of a guide RNA (gRNA) and the Cas9 endonuclease. Cas9 identifies a protospacer adjacent motif (PAM) on the DNA, then binds the complementary sequence guided by the gRNA and causes a double-strand break (DSB). (Barrangou & Doudna, 2016).

The DSB can be repaired through non-homologous end joining (NHEJ), typically

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resulting in gene disruption, or via homology-directed repair (HDR), which allows for precise insertion or correction using a donor template (Ahumada-Ayala et al., 2023; Guo et al., 2022; Lim & Kim, 2022). More recent approaches, such as base editing and prime editing, further enable precise nucleotide changes without the need for DSBs, thereby improving specificity and minimizing cytotoxicity (Ahumada-Ayala et al., 2023; Chehelgerdi et al., 2024; Foss et al., 2019).

In gene therapy, CRISPR is applied *ex vivo* to modify patient-derived cells (e.g., T cells or hematopoietic stem cells) or *in vivo* via direct delivery using viral vectors or lipid nanoparticles (Fellmann et al., 2017; Foss et al., 2019; Lim & Kim, 2022).

CRISPR platforms have evolved significantly since their discovery, with a focus on improving editing precision, delivery efficiency, and therapeutic safety. Engineered Cas9 variants with altered protospacer-adjacent motif (PAM) preferences or reduced off-target activity have enhanced targeting specificity (Barrangou & Doudna, 2016; Guo et al., 2022; Uddin et al., 2020). Additional Cas enzymes (e.g., Cas12a, Cas13) expand the editing scope to include RNA and epigenetic regulation (Chehelgerdi et al., 2024; Foss et al., 2019).

Delivery systems have evolved from viral vectors (e.g., AAVs) to non-viral methods, including lipid nanoparticles and electroporation (Chehelgerdi et al., 2024; Guo et al., 2022). Inducible CRISPR systems, including chemically or optically controlled variants, offer greater spatiotemporal control (Guo et al., 2022). Moreover, base editors and prime editors enable single-base changes or small insertions/deletions without DSBs, reducing genotoxic risk and expanding clinical utility (Ahumada-Ayala et al., 2023; Foss et al., 2019; Guo et al., 2022).

CRISPR is under clinical evaluation across multiple therapeutic areas. In hemoglobinopathies, *ex vivo* CRISPR-edited stem cells (e.g., CTX001) targeting

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BCL11A have enabled transfusion independence in patients with β-thalassemia and sickle cell disease (Chehelgerdi et al., 2024; Uddin et al., 2020). In oncology, CRISPR-engineered T cells with PD-1 knockout or universal CAR insertion are being investigated in early-phase trials (Chehelgerdi et al., 2024; Uddin et al., 2020). *In vivo* gene editing has reached the clinic for transthyretin amyloidosis (NTLA-2001), with promising reductions in serum transthyretin levels (Morshedzadeh et al., 2024).

Other emerging applications include HIV treatment via CCR5 disruption, retinal disease correction, and potential interventions in neurodegenerative and metabolic disorders (Barrangou & Doudna, 2016; Guo et al., 2022; Morshedzadeh et al., 2024; Sun et al., 2020). However, challenges such as off-target effects, delivery efficiency, and immunogenicity remain critical barriers to the widespread clinical translation (Chehelgerdi et al., 2024; Cheng et al., 2020; Morshedzadeh et al., 2024; Uddin et al., 2020).

2.1.3 Cell therapy

Cell therapy encompasses a wide range of approaches, encompassing both stem cell–based and non–stem cell–based products, as well as unicellular and multicellular modalities. These therapies differ in their cellular profiles, isolation methods, mechanisms of action, and regulatory oversight (El-Kadiry et al., 2021).

This study has selected three unicellular modalities, two stem cell-based and one non-stem cell-based, for further discussion: mesenchymal stem cells, natural killer cells, and induced pluripotent stem cells.

Mesenchymal Stem Cell (MSC)

MSCs are multipotent, non-hematopoietic stromal cells initially discovered in the

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bone marrow. They are now present in numerous tissues such as adipose tissue, the umbilical cord, placenta, fetal liver, muscle, dermis, and others. (Bobis et al., 2006; Kobolak et al., 2016). Adipose tissue is regarded as one of the richest sources of MSCs. (Kobolak et al., 2016).

The International Society for Cellular Therapy (ISCT) defines MSCs based on three criteria: plastic adherence under standard culture conditions; expression of CD73, CD90, and CD105 (but not markers related to hematopoiesis, such as CD34 or CD45); and the capacity to differentiate into osteoblasts, adipocytes, and chondrocytes (Bobis et al., 2006; Kobolak et al., 2016; Sensebe et al., 2010; Wang et al., 2022). MSCs have also demonstrated the potential to differentiate into cardiac, neural, hepatic, and endothelial cells (Barry, 2003; Sensebe et al., 2010).

Their therapeutic applications are primarily attributed to:

- Paracrine effects: MSCs release bioactive molecules that aid tissue repair, decrease inflammation, and encourage new blood vessel growth (Barry, 2003; Pittenger et al., 2019; Wang et al., 2012).
- Immunomodulatory functions: They suppress immune cell proliferation and exhibit low immunogenicity, enabling allogeneic use (Barry, 2003; Kobolak et al., 2016; Lai et al., 2011).
- Homing capability: MSCs can migrate to sites of inflammation or injury after systemic administration (Bobis et al., 2006; Wang et al., 2012).

Research into MSCs has grown substantially, with over half of all related publications appearing between 2017 and 2021 (Wang et al., 2022). The therapeutic focus has shifted from direct cell replacement to their paracrine and immunomodulatory effects (Lai et al., 2011; Pittenger et al., 2019).

MSC-derived exosomes (MSC-Exos) have garnered attention as a cell-free

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therapeutic approach, capable of delivering proteins, mRNAs, and microRNAs to target cells (Lotfy et al., 2023; Wang et al., 2022). While promising for improved safety and bioactivity, challenges remain in manufacturing, stability, and standardization (Lotfy et al., 2023; Wang et al., 2022).

Over 950 clinical trials have investigated MSCs, involving more than 10,000 patients. Most studies report favorable safety profiles with limited adverse events (Pittenger et al., 2019; Wang et al., 2012).

Key applications include:

- Graft-versus-host disease (GVHD): MSCs are approved in countries such as Canada and New Zealand for steroid-refractory GVHD (Kobolak et al., 2016; Lotfy et al., 2023; Sensebe et al., 2010; Wang et al., 2012).
- Cardiovascular diseases: Used to treat heart failure and myocardial infarction by enhancing repair and reducing fibrosis (Barry, 2003; Pittenger et al., 2019; Wang et al., 2012).
- Liver diseases: Shown potential in cirrhosis and acute liver failure; MSC-Exos are also under study (Kobolak et al., 2016; Sensebe et al., 2010; Wang et al., 2012).
- Bone and cartilage repair: Applied in osteoarthritis and bone defects due to their osteogenic and chondrogenic potential (Barry, 2003; Bobis et al., 2006; Sensebe et al., 2010).
- Wound healing: MSCs promote angiogenesis and tissue regeneration in skin and corneal injuries (Bobis et al., 2006; Sensebe et al., 2010).
- Neurological diseases: Investigated in stroke, spinal cord injury, and neurodegenerative diseases, such as Parkinson's and Alzheimer's (Lotfy et al., 2023; Sensebe et al., 2010; Wang et al., 2012).

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- Autoimmune diseases: Their immunosuppressive properties make them promising for rheumatoid arthritis, lupus, IBD, and multiple sclerosis (Kobolak et al., 2016; Lotfy et al., 2023; Sensebe et al., 2010).

Future directions focus on exosome-based therapies, improved delivery strategies, and deeper exploration of MSC immunobiology (Wang et al., 2022).

Natural Killer Cell (NK Cell)

NK cells are innate immune lymphocytes that have both cytotoxic and immunoregulatory roles (Caligiuri, 2008; Vivier et al., 2008). Unlike T or B cells, they do not require prior sensitization. They can directly eliminate virus-infected or malignant cells through the release of granzyme B and perforin, via the activation of death receptors (Liu et al., 2021). They also mediate antibody-dependent cellular cytotoxicity (ADCC) through CD16 and secrete cytokines such as IFN-γ and TNF-α to shape adaptive immunity (Liu et al., 2021; Shin et al., 2020).

Their activity is controlled by a balance of activation signals (e.g., NKG2D, NKp30) and inhibitory (e.g., KIRs, NKG2A) receptors that assess MHC-I expression (Shin et al., 2020; Vivier et al., 2008). Loss of MHC-I on tumor cells (“missing self”) or expression of stress ligands (“induced self”) triggers NK cell activation (Vivier et al., 2008).

In cell therapy, NK cells are attractive due to their low risk of GVHD and potential for allogeneic “off-the-shelf” use (Dash et al., 2024; F. Fang et al., 2019; Myers & Miller, 2021). They can be derived from peripheral or cord blood, NK-92 cell lines, or iPSCs (Dash et al., 2024; Myers & Miller, 2021). Genetic modifications, such as CAR expression or cytokine support (e.g., membrane-bound IL-15), further enhance their antitumor activity, persistence, and tumor infiltration (Dash et al., 2024; Shin et al., 2020).

Clinical trials are evaluating NK cell therapies for hematologic cancers (e.g., acute

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myeloid leukemia, lymphoma, and multiple myeloma) and solid tumors (e.g., glioblastoma, ovarian, and lung cancers) (Bald et al., 2020; Liu et al., 2021; Myers & Miller, 2021; Page et al., 2024; Shin et al., 2020). Challenges include short *in vivo* persistence, limited infiltration in solid tumors, and immunosuppressive tumor microenvironments (Jorgensen et al., 2025; Liu et al., 2021; Myers & Miller, 2021). Despite this, NK cell-based immunotherapy is advancing rapidly, supported by innovations in engineering, delivery, and combination strategies.

Induced Pluripotent Stem Cell (iPSC)

iPSCs are reprogrammed adult somatic cells that achieve pluripotency via the ectopic expression of transcription factors (OCT4, SOX2, KLF4, c-MYC) (Doss & Sachinidis, 2019; Singh et al., 2015). Similar to embryonic stem cells (ESCs), they can differentiate into any somatic cell type, offering a versatile platform for regenerative medicine (Baghbaderani et al., 2016; Poetsch et al., 2022).

iPSCs have become a promising cell source for both autologous and allogeneic cell therapy applications. Autologous iPSC therapies reduce immune rejection risks by utilizing the patient's own cells and are under investigation for conditions like Parkinson's disease and age-related macular degeneration (Cerneckis et al., 2024; Doss & Sachinidis, 2019). Allogeneic approaches, utilizing HLA-homozygous donor cells from biobanks, enable off-the-shelf products but face challenges related to immune compatibility (Cerneckis et al., 2024; Doss & Sachinidis, 2019).

Recent developments focus on improving iPSC derivation, genetic stability, and differentiation efficiency (Paes et al., 2017; Poetsch et al., 2022). Safer, integration-free reprogramming methods, such as Sendai virus or episomal plasmids, are now the standard for clinical-grade iPSC production (Doss & Sachinidis, 2019; Negoro et al., 2017; Singh

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et al., 2015). Biobanks storing HLA-matched iPSC lines are being established globally to support the development of scalable therapies (Baghbaderani et al., 2016; Singh et al., 2015).

However, challenges remain. iPSC-derived cells often exhibit immature phenotypes, increasing the risk of tumor formation (Poetsch et al., 2022; Xu et al., 2023). Strategies such as cell sorting, suicide gene systems, and 3D organoid cultures are being explored to improve safety and functionality (Doss & Sachinidis, 2019; Poetsch et al., 2022). Comprehensive quality control for genetic integrity and tumorigenicity is essential for clinical use.

iPSCs are being tested in clinical trials for retinal diseases, spinal cord injuries, heart failure, and neurodegenerative disorders (Doss & Sachinidis, 2019; Sugai et al., 2021). They also offer powerful platforms for disease modeling, drug discovery, and toxicity testing, particularly for rare or complex conditions (Cerneckis et al., 2024; Doss & Sachinidis, 2019). As protocols mature, iPSCs are anticipated to be crucial in advancing personalized regenerative medicine (Cerneckis et al., 2024; Doss & Sachinidis, 2019; Singh et al., 2015).

2.2 Challenges of CGTs to the Current System

Unlike conventional molecular or biologic drugs, CGTs have created a completely different concept for the pharmaceutical industry. In the past, the goal of developing a drug was to find a solution for everyone. However, the essence of CGT is to create a single solution for a particular individual, making it difficult to scale up or reduce costs. This section aims to discuss the key features that contribute to CGTs' difficulties in the payment system.

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2.2.1 Clinical Uncertainty and Safety Challenges

CGTs often face significant clinical development challenges due to small patient populations and inherent uncertainties in long-term safety and efficacy. The development of CGTs is further delayed because the therapy usually targets rare and monogenic diseases (Zhang & Wu, 2024), making it difficult to fulfill conventional clinical trial standards. For instance, the pivotal trial for Glybera involved only 27 participants, illustrating the limited scale of many CGT studies. The rarity and severity of the targeted diseases, often genetic or life-threatening, further complicate the generation of robust clinical evidence. These constraints make it particularly difficult to establish benefit-risk profiles in early-stage trials and have led to a growing emphasis on the systematic collection of real-world evidence (RWE) post-approval (Lee & Lee, 2023; Riva & Petrini, 2019; Watanabe et al., 2015).

Safety concerns remain a central issue throughout CGT development and post-market surveillance. Reports of secondary malignancies following CAR-T therapy have emerged, highlighting the need for continued monitoring. Vector-related immunogenicity and dose-dependent toxicity, such as those associated with AAV vectors, are also notable risks. Cases of clonal T-cell proliferation have been observed in SCID-X1 gene therapy, and thrombotic microangiopathy has been reported after gene therapy for spinal muscular atrophy (SMA). Additionally, CAR-T therapies are associated with severe adverse events such as cytokine release syndrome (CRS) and neurotoxicity (Cring & Sheffield, 2022; Kohn et al., 2023).

Given these complexities, early-phase CGT trials often require tailored, case-specific designs that differ substantially from conventional drug development models. Even after regulatory approval, ongoing challenges persist in ensuring sustained safety and therapeutic benefit (Cring & Sheffield, 2022).

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Due to the mechanism and side effects of CGT, conducting placebo-controlled or blinded trials is particularly challenging, making it difficult to distinguish between product effects and the natural progression of the disease, placebo effects, and observational bias.

CGTs carry potential risks associated with genetic modification, such as immune responses or delayed adverse events. As a result, several regulatory guidelines mandate long-term safety monitoring for patients receiving CGTs. For instance, India's guidance explicitly requires long-term follow-up, although it does not specify the duration or clarify how such requirements affect the evidentiary threshold during regulatory review (Dalal et al., 2023); the US FDA requires patients who receive gene therapies to be followed for 15 years (Elverum & Whitman, 2020). This implies that, at the time of initial marketing authorization, long-term data on safety and efficacy may still be immature or unavailable. Regulatory authorities are thus required to assess the benefit-risk profile of a product under conditions of limited longitudinal evidence. In some regions, such as Japan, a conditional approval pathway is employed, permitting market entry for therapies that demonstrate preliminary safety and efficacy and address unmet medical needs, while requiring post-marketing surveillance studies to collect additional data (Maruyama et al., 2023a). This mechanism reflects the underlying uncertainty in evidence at the point of initial submission.

Reimbursement decisions are often complicated by limited long-term efficacy data at the time of market entry. Many gene therapies receive regulatory approval based on surrogate endpoints, requiring post-marketing data collection to confirm clinical benefits (Horrow & Kesselheim, 2023). This uncertainty increases financial risk for payers, leading to delayed reimbursement decisions or restricted coverage.

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2.2.2 Manufacturing, Supply Chain, and Delivery Constraints

The manufacturing of CGTs, particularly those utilizing viral vectors such as AAV or lentivirus, is inherently complex. The production process involves multiple technically demanding steps with stringent quality control. Scale-up production to meet increasing clinical and commercial demand presents significant technical challenges, especially in maintaining product consistency and batch-to-batch reproducibility. Key bottlenecks include the transient transfection of viral vectors and the requirement for high-density cell cultures, both of which add layers of complexity to upstream and downstream processes. Achieving scalable, reproducible, and cost-effective manufacturing remains a critical barrier to the broader availability of CGTs (Jogalekar et al., 2022; Shupe et al., 2022).

Point-of-care manufacturing and academic-led CGT programs also face limitations in accessibility and operational scale. Moreover, disparities in reimbursement policies across countries contribute to uneven access to ATMPs, reinforcing geographic inequities in clinical availability. For example, even in well-resourced systems, the clinical integration of CAR-T therapies remains hindered by capacity constraints and procedural complexity (Sanchez-Guijo et al., 2024).

The development, delivery, and patient experience of CGTs differ substantially from those of conventional medicines. These therapies vary widely; some are personalized for individual patients, while others target broader populations; some involve human-derived materials, others do not; bioengineering may occur either *ex vivo* or *in vivo*. Elverum and Whitman (2020) have had discussions focused on the most complex category: personalized, autologous, *ex vivo* therapies, such as CAR-T treatments. While the focus is on this subset, many of the insights and structural challenges apply broadly across the CGT landscape, offering a valuable framework for designing delivery systems for future advanced therapies.

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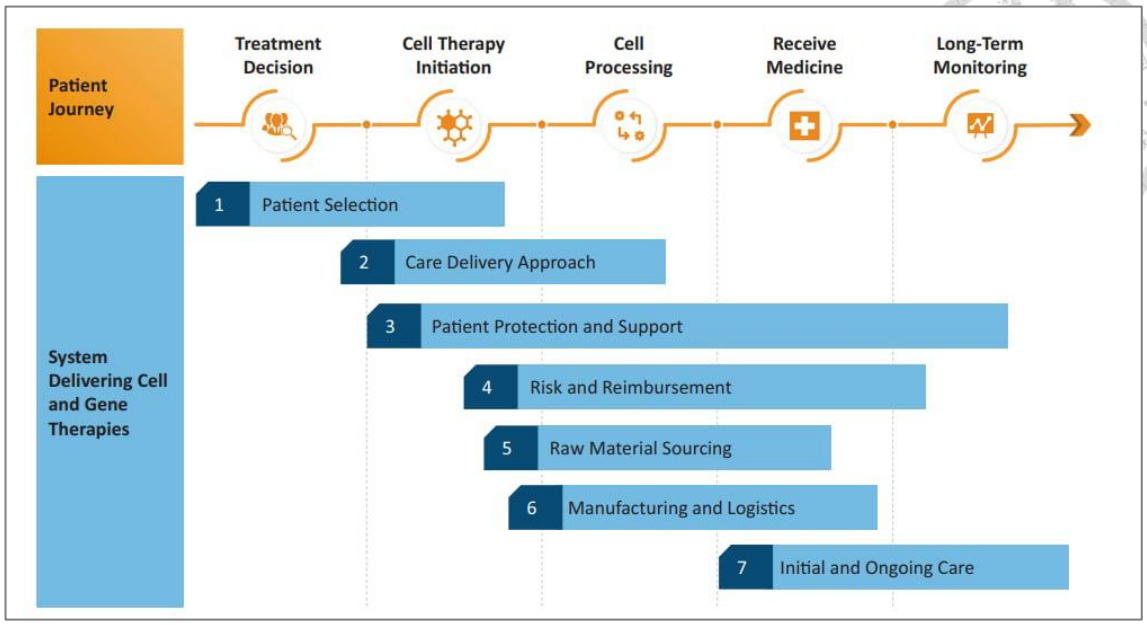

Figure 2-2

System for Delivering Individualized, Autologous, Ex Vivo, Cellular Therapies

Note. Reprinted with permission from "Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine", by Kris Elverum et al, "Gene Therapy", 27, pages 537–544 (https://doi.org/10.1038/s41434-019-0074-7). Copyright 2019 by The Author(s).

The effective delivery of CGTs requires highly specialized infrastructure and a well-trained clinical workforce. CGT therapies involve complex logistical processes, including cell harvesting, manufacturing, and administration, that require tight coordination across multiple settings (Pillai et al., 2020). Currently, only a limited number of treatment centers possess the necessary capabilities, posing significant barriers to patient access. Establishing certification standards for clinical sites, such as those set by the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) and the Foundation for the Accreditation of Cellular Therapy (FACT), has become essential to ensure quality and safety (Pillai et al., 2020; Sanchez-Guijo et al., 2024).

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2.2.3 Payment and Reimbursement Mechanisms

Budget Impact

The complex manufacturing processes result in the high cost of CGT. The reported manufacturing cost per patient during clinical trials ranges from US$100,000 to $300,000 (Elverum & Whitman, 2020). Sabatini and Chalmers (2023) estimated that developing a new cell or gene therapy through clinical-stage R&D requires an investment of approximately US$1.943 billion, which is significantly higher, ranging from 6 to 400 times that of the cost associated with traditional molecular drug development.

The high cost thereby leads to the high listing prices of CGTs, thus posing substantial affordability challenges for both patients and healthcare systems. For example, Glybera was priced at approximately US$1 million, Luxturna at US$850,000, and Zolgensma at around US$2.1 million per treatment (Cring & Sheffield, 2022). Unlike chronic therapies, which distribute costs over time, these one-time therapies come with significant upfront costs. CGT employment is further complicated by clinical uncertainty regarding long-term safety issues and budgetary challenges for both public and private payers (Horrow & Kesselheim, 2023; Kohn et al., 2023; Lopata et al., 2023; Phares et al., 2024).

Traditional payment models based on single, upfront reimbursement are often ill-suited to CGTs, as the financial risk is concentrated at the point of administration. If treatment fails, the resulting societal and payer losses are considerable.

Moreover, existing reimbursement frameworks, such as the “best price” rule under Medicaid in the United States, may hinder the adoption of innovative value-based payment models, including outcomes-based agreements or installment-based financing. Payers, such as self-insured employers and public health programs, are increasingly struggling to manage the high and unpredictable costs linked to CGTs (Phares et al., 2024). The complexity of manufacturing processes also contributes to elevated pricing,

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exacerbating concerns about system-wide affordability and access (Kohn et al., 2023).

Value Assessment and Economic Feasibility

Health technology assessment (HTA) plays a critical role in the market access of CGTs, with institutions such as the Institute for Clinical and Economic Review (ICER) in the United States conducting evaluations to inform coverage and pricing decisions. In countries like South Korea, HTA outcomes and pricing negotiations are also influenced by international benchmarks, including reference prices from the EU5, the United States, and Japan (Hampson et al., 2018; Lee & Lee, 2023). However, assessing the value of CGTs presents unique challenges. Given their one-time administration, small patient populations, and clinical uncertainty, it is challenging to apply conventional pharmacoeconomic (PE) frameworks to evaluate cost-effectiveness. Traditional methods, like models based on quality-adjusted life years (QALYs), might not completely reflect the long-term therapeutic benefits of CGTs. The limited bed availability of mature clinical data further complicates efforts to demonstrate sustained benefits and cost-effectiveness, thereby raising barriers to reimbursement and adoption (Denise T Kruzikas et al., 2020; Lee & Lee, 2023).

CGTs expose a misalignment between upfront costs and long-term clinical outcomes within current funding models. As many of these therapies are administered only once yet deliver benefits over a patient's lifetime, risk-sharing reimbursement mechanisms become essential, requiring supportive policy and regulatory frameworks to enable their implementation (Elverum & Whitman, 2020).

2.3 Global Responses to CGT Payment Challenges

This section examines how the United States, the European Union, and Japan have

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responded to the payment and regulatory challenges posed by CGT. Innovative payment solutions have been widely discussed (see 2.3.1), but the situation may vary across different countries with varying healthcare systems. The discussion at the national level mostly focuses on a single country or system; comparisons between multiple nations or systems are rare.

2.3.1 The Innovative Payment Models for CGT

To address the high initial costs, uncertain long-term outcomes, and sustainability concerns associated with CGT, various innovative payment models have been proposed and implemented across different healthcare systems. As shown in **Table 2-2**, these models can be categorized into four main strategic approaches: amortization, risk spreading, performance-based payments, and real-world evidence-linked pricing. Each approach includes specific payment models, such as installment payments, outcome-based contracts, or subscription pricing, that reflect attempts to balance the financial burden among stakeholders. The advantages and disadvantages of each model vary significantly depending on the perspective of the manufacturer, patient, or payer.

For instance, outcome-based payments may ensure better alignment between price and therapeutic effectiveness, yet their implementation requires complex tracking infrastructure and incurs additional transaction costs. Risk-pooling strategies help diffuse financial exposure across payers but may reduce patient accessibility when risk pools are limited. Installment payment plans under amortization can reduce the initial budget impact but may result in payers covering ineffective treatments. This comparative mapping highlights not only the diversity of mechanisms under experimentation but also underscores the challenges of aligning incentives across stakeholders in the context of CGT reimbursement. The warranty includes coverage purchased by the manufacturer to

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a third-party insurance party, with the payer as a beneficiary. If repeated dosing is possible, the manufacturer could commit to providing subsequent doses for free if the treatment effect wanes over time (Horrow & Kesselheim, 2023).

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Table 2-2

Types of Innovative Payment Models for Cell and Gene Therapy

Approaches	Strategies	Payment Models	Stakeholders					
			Manufacturer		Patient		Payer	
Amortization	Divide Payments Over Time	Installment Payments					✓ ✕ ✕	Reduce the pressure of a large upfront payment May be paying for ineffective treatments Patients may switch to different payers
Risk Spreading	Share Costs with Other Payers	Risk Pool or Reinsurance			✕	The size of the pool is limited, reducing patient accessibility	✓ ✓	Patient movement within the same risk pool or under a shared reinsurer does not impact payers Financial risk is distributed to a mass of people or transferred to third parties
	Cap Costs Based on Expected Patient Volume	Price-Volume Agreement	✕	High-manufacturing-cost products	✓	Patients' accessibility increases (especially for communicable or chronic diseases)	✓	Separate costs from individual patients to reduce manufacturer incentives for overpromotion.
		Subscription	✓	Guaranteed revenue				
Performance-Based Payment	Adjust Price Based on Individual Patient Outcomes	Outcome-Based Payments or Outcome-Based Rebates/Milestone-Based Contract					✕	Tracking outcomes and adjusting payments is costly and complex; third-party support helps but adds system costs.
		Warranty	✕	Possible additional expenditure	✓	The risk of unpredictable treatment outcomes due to individual variability can be compensated.	✓ ✕	The risk of unpredictable treatment outcomes due to individual variability can be compensated. Tracking outcomes and adjusting payments is costly and complex; third-party support helps but adds system costs.
	Adjust Price Based on Real-World Evidence	Population Outcomes-Based Agreement or Coverage With Evidence Development	✓ ✓ ✕	Enables flexibility in handling missing individual data Allows inclusion of diverse outcome measures in reevaluation Outcomes depend on data completeness and the alignment between the payer's patient population and the reference group			✕	Smaller payers lack sufficient leverage to request studies addressing their specific concerns

Note. Adapted from Horrow and Kesselheim (2023), Lopata et al. (2023), and compiled by the researcher. ✓ represents the advantages that the strategy or payment model might bring to the stakeholder group, and ✕ represents the disadvantages.

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2.3.2 The United States

Fragmentation of Health Coverage in the United States

The United States adopts a fragmented healthcare financing model that lacks a unified national insurance system. As of 2023, approximately 65.4% of the population had private insurance, primarily through employer-sponsored plans, while 36.3% were enrolled in public programs, such as Medicare and Medicaid (US Census Bureau, 2024). Medicaid, in particular, has expanded its coverage and fiscal responsibility, enrolling over 100 million individuals through state-based programs and insurance marketplaces (Office of the Assistant Secretary for Planning and Evaluation, 2025). This tripartite structure, comprising Medicare, Medicaid, and private insurers, creates a heterogeneous environment for reimbursement decisions, where payer-specific criteria and regulatory discretion lead to uneven patient access across states and insurance types.

Figure 2-3 demonstrates the health care spending by each payer in the United States, demonstrating that no type of payer has been the dominant one.

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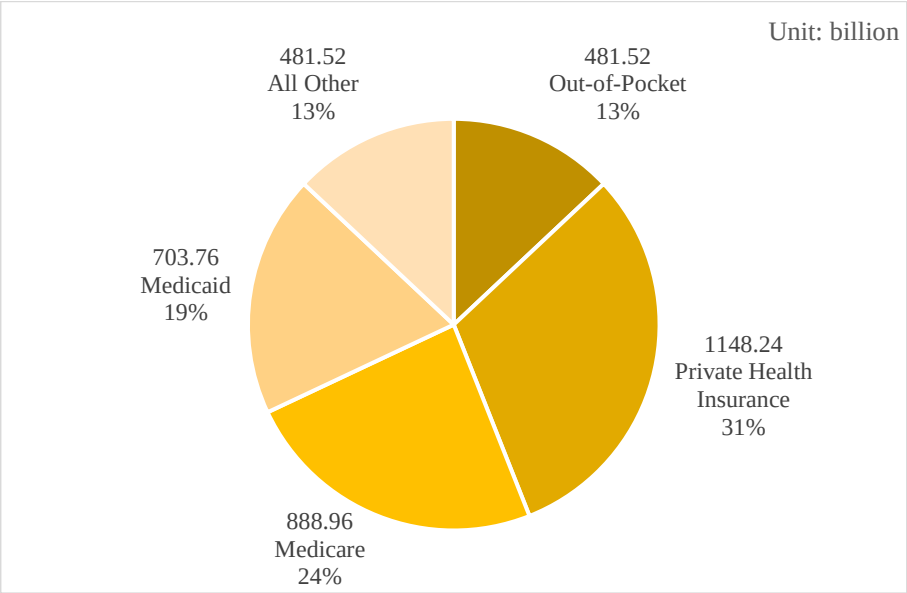

Figure 2-3

Personal Health Care Spending by Payer in the United States (2022)

Note. Adapted from Rudowitz et al. (2024) and compiled by the researcher.

Institutional Barriers to Reimbursement of High-Cost Therapies

Since the FDA approval of Kymriah in 2017, the first CAR-T therapy designed as a one-time, curative treatment, it has become increasingly evident that the current US reimbursement system, which was initially designed for chronic, incrementally dosed treatments, needs new models to cope with the entirely new therapy and the doubts or risks it may bring along (Bach et al., 2017).

As highlighted by Berry et al. (2025), this structural misalignment imposes considerable financial strain on both public and private payers, particularly given the limited availability of long-term clinical and economic outcome data at the time of launch. The challenge is exacerbated by high patient mobility across insurance plans, which undermines payer incentives to cover costly therapies whose benefits may not increase during a given plan's coverage period.

The reimbursement of high-cost innovative therapies in the United States is subject

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to distinct institutional constraints. Medicare, Medicaid, and private insurance will be discussed in this section, and a comparison of the three payers is displayed in **Table 2-3**.

1. Medicare

Medicare plays a central role in financing high-cost therapies in the United States, particularly through its Part B and Part D programs[1]. Within the Medicare program, coverage decisions are governed by the Centers for Medicare & Medicaid Services (CMS) and must meet the criterion of being "reasonable and necessary" (CMS, 2024). For CAR-T therapy, CMS issued a National Coverage Determination (NCD) in 2019, allowing reimbursement under specified clinical conditions and mandating participation in a Coverage with Evidence Development (CED) program to collect real-world outcomes data (CMS, 2019).

Although CGTs are not yet dominant in Medicare drug spending, their high unit cost and hospital-based administration suggest they will increasingly fall under Part B reimbursement. However, the existing reimbursement structures often lack the flexibility to accommodate innovative, outcome-dependent treatments such as CGTs. While past attempts to reform drug pricing under Medicare, such as the Most Favored Nation (MFN) Model and the Part B Drug Payment Model, sought to reduce spending through aggressive price controls, they encountered significant political and legal obstacles and were ultimately rescinded (Liu et al., 2024). These failures highlight the limitations of top-down, mandatory reforms in complex therapeutic areas, such as CGT, where pricing must reflect both clinical uncertainty and individualized outcomes.

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[1] Parts of Medicare include Part A (Hospital Insurance), Part B (Medical Insurance), and Part D (Drug Coverage).
Source: https://www.medicare.gov/basics/get-started-with-medicare/medicare-basics/parts-of-medicare (Accessed on June 22, 2025)

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2. Medicaid

Medicaid, on the other hand, demonstrates significant heterogeneity across states due to decentralized administration and varying fiscal capacities. Beinfeld et al. (2023), Allen et al. (2023), and Berry et al. (2025) have concluded that Medicaid programs in different states are applying varying criteria and coverage indications, resulting in delayed access to therapy for patients. These restrictions often involve criteria such as patient failure, life expectancy, genetic markers, and prior treatments. The greatest variability was observed in policies for AAV gene therapies and CAR-T therapies.

To address these coverage barriers, they propose a range of federal policy interventions. These include issuing clearer guidance to states on coverage expectations, improving transparency through public dashboards, and establishing mechanisms to report non-compliance. Additionally, financial reforms such as value-based payment models, enhanced federal cost-sharing, and mechanisms for states to preview upcoming therapies are recommended to help states manage the substantial up-front costs of CGTs. Collectively, these strategies aim to reduce administrative delays, align state practices with federal intent, and ensure equitable access to innovative therapies across the Medicaid landscape (Allen et al., 2023).

On the other hand, the Medicaid Drug Rebate Program (MDRP), particularly its "Best Price" provision, presents significant challenges to implementing value-based payment models for CGTs. Under current rules, a single deeply discounted commercial transaction can trigger nationwide Medicaid rebate obligations, discouraging manufacturers from offering outcome-based contracts. This is particularly problematic for rare conditions, where small patient populations amplify the risk of rebate volatility. Besides, limitations such as a three-year rebate adjustment window and the

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misinterpretation of installment payments as full prices further hinder innovative financing models (Quinn et al., 2023).

The CMS introduced reforms in 2020 that allow manufacturers to report "Multiple Best Prices" based on performance tiers or use average pricing under "Bundled Sales" (CMS, 2020). Simulations by Quinn et al. (2023) indicate that the Multiple Best Prices approach is the most effective at expanding Value-based purchasing arrangements (VBPAs) coverage and minimizing payment misalignment. Compared to other models, it offers greater flexibility for manufacturers without exposing them to excessive Medicaid rebate liabilities.

However, in reply to the 2022 executive order aimed at reducing drug use costs, the Center for Medicare and Medicaid Innovation (CMMI) also proposed "the Cell and Gene Therapy Access Model" as one of three innovative drug payment demonstrations in 2023 (CMS, 2023). Recognizing the substantial clinical promise and high upfront costs of CGTs, this voluntary model facilitates access for state Medicaid programs by enabling CMS to negotiate and administer outcomes-based agreements on behalf of a multi-state purchasing pool. Under this arrangement, payment levels to manufacturers would be contingent upon real-world therapeutic outcomes, creating a framework that aligns pricing with clinical effectiveness and mitigates budget impact uncertainties. Although CMMI has no prior experience implementing Medicaid drug payment models and institutional challenges, the newly proposed CGT Access Model offers a promising opportunity to leverage pooled bargaining power and centralized outcome-based contracting to improve patient access while encouraging pricing accountability in the emerging market of CGTs (Horrow & Kesselheim, 2023; Liu et al., 2024).

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3. Private Insurance

In private insurance markets, decisions regarding the coverage of emerging therapies are typically informed by HTAs, economic evaluations, and market considerations. Although regulatory approval is a prerequisite for coverage eligibility, insurers may introduce additional clinical criteria or usage restrictions. The financial impact of high-cost therapies also compels insurers to consider strategies such as value-based agreements, phased payments, or reinsurance arrangements to mitigate potential risks (Bach et al., 2017). However, the practicality of these mechanisms is frequently limited by the availability of outcome data and the payer's negotiation strength.

Table 2-3

Comparison of Coverage Criteria and Access Conditions for High-Cost Therapies Under the United States Insurance Models

	Medicare	Medicaid	Private Insurance
Coverage Criteria	Reasonable and Necessary + CED	Determined by state governments, highly variable	Internal HTA evaluation and market strategy
Speed of Inclusion	Moderate; requires CMS evaluation and decision	Slow and inconsistent	Potentially fast, but with possible restrictions
Price Negotiation	No explicit mechanism (Medicare lacks negotiation power)	Negotiable at the state level, but with limited leverage	Negotiable. Performance-based payment agreements may be adopted
Patient Accessibility	Relatively high (especially for those aged 65 and above)	Varies by region; low-income and minority groups may lack access	Depends on policy terms and the insurer's risk management strategies

Note. Compiled by the researcher from Allen et al. (2023), CMS (2019), Alliance for Regenerative Medicine (2023b), and Tunis et al. (2021). CED=coverage with evidence development; HTA = health technology assessment; CMS = the Centers for Medicare & Medicaid Services.

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Overall, the integration of expensive medical innovations into insurance systems reveals systemic differences in how financial risk, clinical evidence, and access equity are managed. Public programs, while more standardized at the federal level, may still be subject to administrative limitations and political variation. In contrast, private insurers operate with greater flexibility but also exhibit variability that may exacerbate disparities in access to advanced therapies.

Current academic discourse on CGTs and the US payment system mainly focuses on the challenges faced by public insurance and the reforms needed to address them. A general agreement is observed on shifting toward value-based or outcome-based payment models. It is considered a strategy to mitigate payer risk, enhance patient access, and maintain incentives for innovation. Such models can help spread financial burdens over time while aligning payments more closely with real-world treatment effectiveness (Zhang & Shugarman, 2024). In addition, Zhang and Shugarman (2024) propose the establishment of a publicly funded special plan to support the sustainable financing of CGTs within the fragmented US insurance system.

Still, several reforms are already underway, and the effectiveness of these changes and their impact on improving patient access to new therapies remain uncertain, requiring further observation and analysis.

2.3.3 The European Union

Payment and reimbursement decisions in the EU are primarily made at the national level (Iglesias-Lopez et al., 2023; Mahalatchimy et al., 2024). HTA is a key process in EU countries for deciding whether to include new treatments in their national healthcare systems (Aitken et al., 2024; Alliance for Regenerative Medicine (ARM), n.d.; Iglesias-Lopez et al., 2023).

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CGTs often have limited clinical data available at the time of marketing. The evidence from single-arm studies, short-term trials, or small patient groups is not sufficiently developed, leading to high uncertainty regarding their long-term efficacy, safety, and cost-effectiveness (Aitken et al., 2024; ARM, 2023a, n.d.; Iglesias-Lopez et al., 2023; Ronco et al., 2021). Additionally, traditional HTA methods are designed for conventional drugs. They are not suitable for ATMPs that may "cure" rare or ultra-rare diseases due to their one-time treatment, long-term benefits, and high upfront costs, making evaluations challenging (Ronco et al., 2021; Velikanova et al., 2024). For example, generic health-related quality of life HRQoL scales (such as EQ-5D) may not completely reflect the actual decline in quality of life experienced by patients with rare diseases, resulting in underestimated benefits (ARM, n.d.). Notably, there are differences in the perceived levels of clinical uncertainty and potential additional benefits among European countries, leading to inconsistent HTA evaluations and reimbursement decisions for the same CGTs (Callenbach et al., 2024; Carvalho et al., 2021; Desmet et al., 2024). This increases the complexity of market access for manufacturers and different list prices throughout the region, as discussed by Aitken et al. (2024), Western Europe tends to reimburse a higher percentage of CGTs compared to Eastern Europe.

To address these issues, the EU has made several changes to improve the situation:

- Accepting higher levels of uncertainty: HTA agencies are observed to be more willing to accept higher levels of uncertainty in clinical and economic evidence, and are flexible in adjusting their assessment methods (ARM, n.d.).
- Incorporating real-world evidence (RWE): More countries are integrating RWE into their assessments to handle uncertainties regarding long-term efficacy and safety better. The EU is working to establish a pan-European real-world data (RWD) registry (Carvalho et al., 2021; Jorgensen et al., 2020;

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Rejon-Parrilla et al., 2023).

- Considering longer assessment timeframes and societal perspectives: As CGTs may bring long-term benefits, HTA agencies are beginning to extend the scope of assessments to longer periods and consider broader societal benefits, such as the impact on patient productivity and caregiver burden (ARM, n.d.; Jorgensen & Kefalas, 2015; Rejon-Parrilla et al., 2023).
- EU HTA Regulation (EU) 2021/2282: This regulation, which will be mandatory in 2025, requires ATMPs to undergo a Joint Clinical Assessment (JCA) (European Commission, 2025). The aim is to establish a common scientific foundation for countries and to accelerate patient access to innovative treatments. However, pricing and reimbursement decisions remain a national responsibility (ARM, n.d.; Mahalatchimy et al., 2024).
- Infrastructure development:
    - Specialized treatment centers: The complexity of CGTs requires specialized treatment centers, well-trained personnel, and a rigorous logistics chain. The UK has established a network of Advanced Therapy Treatment Centers (ATTCs) (Jorgensen & Kefalas, 2015; Pillai et al., 2020; Velikanova et al., 2024).
    - International certification (JACIE): JACIE certification helps ensure quality management systems in the field of CGT (Sanchez-Guijo et al., 2024).
    - Hospital Exemption (HE): EU legislation permits the use of unauthorized ATMPs under specific conditions, like unmet medical needs, via the “hospital exemption” pathway, offering an alternative access route (Fischer et al., 2023; Lee & Lee, 2023; Sanchez-Guijo

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et al., 2024).

Regarding reimbursement and pricing, some payers benchmark CGT prices against off-label or non-patented best supportive care, potentially undervaluing innovation and driving products off the market (ARM, 2023a). Furthermore, external reference pricing across countries further limits pricing flexibility (Jorgensen & Kefalas, 2015; Lee & Lee, 2023; Rejon-Parrilla et al., 2023). Moreover, the confidentiality surrounding Managed Entry Agreements (MEAs) in many countries hinders transparency, knowledge sharing, and the dissemination of best practices (Desmet et al., 2024; Jorgensen & Kefalas, 2015; Rejon-Parrilla et al., 2023; Ronco et al., 2021).

Some products have been pulled from the market due to failed pricing negotiations, rather than a lack of efficacy, as seen with Glybera, Skysona, and Zynteglo in the EU, highlighting the critical role of pricing negotiations in ensuring patient access (Mohan et al., 2025). Specific measures have been adopted to cope with pricing challenges:

- Early dialogue and collaboration: Early dialogue between manufacturers and payers is considered critical for building consensus on evidence requirements and payment models, thereby shortening the time to market (Jorgensen et al., 2020; Velikanova et al., 2024).
- Price discounts and rebates: Many countries utilize financial agreements, such as discounts, rebates, and price caps, to mitigate budget impacts (Jorgensen et al., 2020; Rejon-Parrilla et al., 2023; Ronco et al., 2021).
- Germany's free pricing period: Germany allows new therapies to be priced freely for 12 months after launch (now reduced to 6 months), after which price negotiations are held (Fischer et al., 2023; KOÇKAYA et al., 2020).
- Special funds and early access programs:
    - UK: The Cancer Drugs Fund (CDF) and the Innovative Medicines

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Fund (IMF) were established to provide temporary funding for uncertain but promising therapies while additional evidence is collected (Jorgensen et al., 2020; Rejon-Parrilla et al., 2023).

- France: The "Autorisation Temporaire d'Utilisation (ATU)" program allows patients to receive early treatment and reimbursement before a product receives full marketing authorization (Iglesias-Lopez et al., 2023; Jorgensen et al., 2020).
- Germany: The Risk Pool fund was launched to reduce the financial burden of high-priced ATMPs (Fischer et al., 2023). Hospitals can apply for "New Investigations and Treatments (NUB)" status to receive additional reimbursement on top of existing diagnosis-related group (DRG) fees (Fischer et al., 2023; Lee & Lee, 2023).
- Italy: Establishment of a dedicated fund for innovative drugs and provision of immediate inclusion in regional medical lists (Lee & Lee, 2023; Rejon-Parrilla et al., 2023).

- Cross-border collaborative pricing: Although left mainly to individual countries, some European countries have begun joint HTA assessments and drug price negotiations through alliances, e.g., FINOSE (comprising Finland, Norway, and Sweden) and the Beneluxa Initiative on Pharmaceutical Policy (BeNeLuxA). The European Commission is also working on a joint "European Value Framework" (Iglesias-Lopez et al., 2023; Lee & Lee, 2023; Rejon-Parrilla et al., 2023).

However, despite the critical challenges that CGTs pose to the EU's payment system, the role of private insurance is not addressed much in the literature.

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2.3.4 Japan

In 2014, Japan introduced two significant legislative reforms: the Act on the Safety of Regenerative Medicine (ASRM) and the Pharmaceuticals and Medical Devices Act (PMD Act), both of which have greatly transformed the regulatory environment for regenerative medicine (PMDA, n.d.). The ASRM governs the use of processed cells and licenses external cell processing facilities (Act on the Safety of Regenerative Medicine, 2020). The PMD Act permits conditional, time-limited approval for regenerative products that demonstrate early safety and potential benefits (Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, 1960). These reforms aim to speed up clinical use and commercialization of regenerative therapies (Azuma, 2015).

Under ASRM, “regenerative medicine” refers to medical practices using regenerative technologies, excluding formal clinical trials regulated under the PMD Act. “Regenerative medicine technologies” include:

1. Medical technologies use processed cells, excluding approved regenerative products used strictly within authorized indications.
2. Medical technologies using nucleic acids, also excluding approved drugs and products, when used only within their designated use.

Japan has a universal public health insurance system that mandates enrollment for all Japanese citizens, permanent residents, and non-Japanese residents with a visa valid for three months or more (Okada et al., 2017). Most treatments and diagnostic technologies for diseases are covered by public insurance. In contrast, services unrelated to diseases, such as health examinations, preventive injections, and cosmetic surgery, are paid out of pocket (Okada et al., 2017).

Japan’s National Health Insurance (NHI) system reimburses regenerative products

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that are authorized under the Pharmaceuticals and Medical Devices (PMD) Act, including those with conditional and time-limited approvals:

- Patients pay their co-payment (10% to 30%), but the High-Cost Medical Care Scheme caps their out-of-pocket expenses, significantly subsidizing the high costs of these therapies (Lysaght, 2017; Okada et al., 2017; Umemura & Morrison, 2021).
- Products with conditional, time-limited approval can be listed on the NHI Drug Price List or Medical Material Price List (Azuma, 2015; Lysaght, 2017; Okada et al., 2017). Conditional and Time-Limited Approval was introduced in 2014, enabling regenerative medical products to access the market with sufficient data that predict likely efficacy and confirm safety from early-phase clinical trials, usually within seven years (Azuma, 2015; Maeda et al., 2015). During this period, the marketing authorization holder must further confirm the effectiveness and safety of the product and submit data for full approval, often through post-marketing surveillance or observational studies on all treated patients (Coppens et al., 2018; Maeda et al., 2015). HeartSheet's conditional approval, for instance, was extended by three years due to insufficient enrollment for post-marketing data collection (Arato & Nomura, 2024). Products that fail to demonstrate efficacy within the specified timeframe may have their authorization revoked (Maeda et al., 2015). Several products, including Collategen, Delytact, HeartSheet, and Stemirac, have been marketed only in Japan under this pathway (Arato & Nomura, 2024).

Regenerative medicine therapies offered through clinical research or medical treatment under the Act on the Safety of Regenerative Medicine (ASRM) are typically

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not covered by NHI. They also cannot be combined with treatments covered by other insurance unless they are classified as an Advanced Medical Therapy (Azuma, 2015). For example:

- Under “Chiken” (PMD Act clinical trials), partial insurance coverage can be provided for medical services associated with the trial, but not for the experimental unapproved product itself, particularly in company-sponsored trials (Azuma, 2015; Lysaght, 2017; Okada et al., 2017).
- For “Advanced Medical Care”, treatments designated by the Ministry of Health, Labour and Welfare (MHLW) can be combined with other insurance-covered medical services, even if the innovative treatment itself is not covered by insurance (Azuma, 2015; Lysaght, 2017).

Regarding HTA, Japan's framework is relatively new and not fully mature (Lysaght, 2017). Traditionally, reimbursement assessments for new technologies were based on comparisons with standard care and additional costs, but concepts like “Quality-Adjusted Life Year (QALY)” were not considered (Lysaght, 2017; Okada et al., 2017; Yamada et al., 2025). MHLW began a pilot assessment program in 2016 to integrate HTA in the future (Lysaght, 2017; Okada et al., 2017). Critics argue that the lack of robust efficacy data and a clear HTA system has led to some regenerative medicine products, such as HeartSheet and Temcell, being prematurely listed for public insurance reimbursement at high prices, despite uncertain clinical benefits (Lysaght, 2017; Okada et al., 2017).

In Japan, the pricing of new regenerative medicine products is usually based on a cost accounting approach. The prices of earlier products often impact the pricing of later ones. The final decisions on reimbursement for regenerative medical products are made by the Central Social Insurance Medical Council (CHUIKYO) within the MHLW (Okada et al., 2017).

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Japan has established a national registry system for regenerative medical products, managed by the Pharmaceuticals and Medical Devices Agency (PMDA), to ensure transparency and track the implementation status of regenerative medicine technologies (Maeda et al., 2015). Conditional approvals often require follow-up on all patients to collect data confirming safety and efficacy (Coppens et al., 2018).

There are suggestions for "payment by results" mechanisms for high-cost regenerative medicine products (Umemura & Morrison, 2021). The potentially very high costs of iPSC-based retinal cell therapies may require the implementation of a specialized health insurance system for state-of-the-art medical treatments (Yamada et al., 2025). Multilateral scientific consultation between regulatory agencies and payers is also proposed early in development to ensure patient access to innovative medicines (Coppens et al., 2018).

2.4 Multilevel Frameworks of Technology Management

Understanding the development and diffusion of emerging technologies requires an integrative perspective that spans multiple levels of analysis, including technological, organizational, and institutional (see **Figure 2-4**). This section synthesizes key theoretical frameworks that inform technology management and strategic decision-making, providing a foundation for evaluating the dynamics of novel health technologies such as cell and gene therapies.

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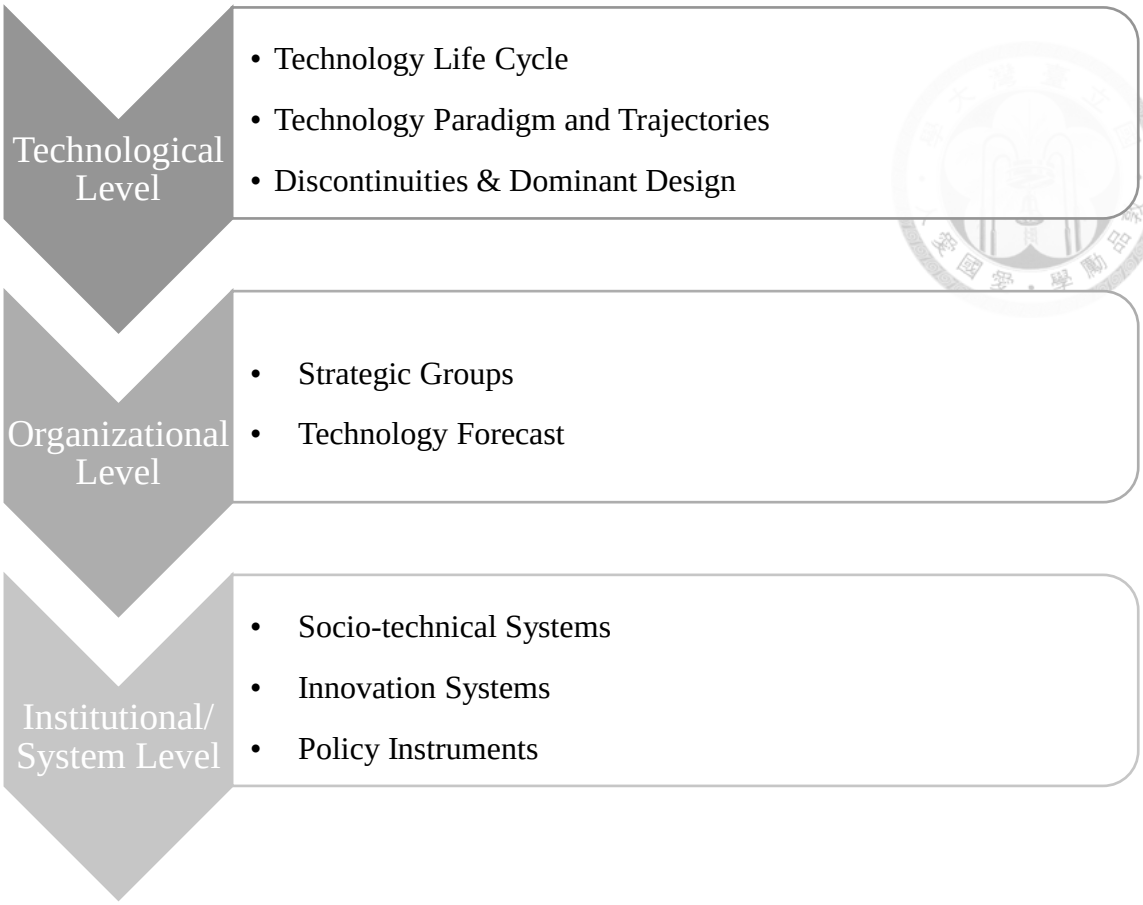

Figure 2-4

Multi-level Theoretical Framework in Technology Management

Note. Synthesis from the researcher based on Dosi (1982), Anderson and Tushman (1990), and Geels (2005).

2.4.1 Technological Evolution: Life Cycles, Paradigms, and Discontinuities

A fundamental concept in technology management is the Technology Life Cycle (TLC), which characterizes the stages of a technology's evolution over time (Taylor & Taylor, 2012). Unlike product or industry life cycles, TLC centers on the technology itself as the unit of analysis. The S-curve representation of TLC (see **Figure 2-5**) highlights the relationship between cumulative R&D effort and technological performance, progressing

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through four primary stages: emergence, growth, maturity, and saturation (Ernst, 1997). In early stages, performance gains are slow despite significant input; during growth, the performance accelerates rapidly; maturity brings stabilization; and saturation signals diminishing returns and potential obsolescence.

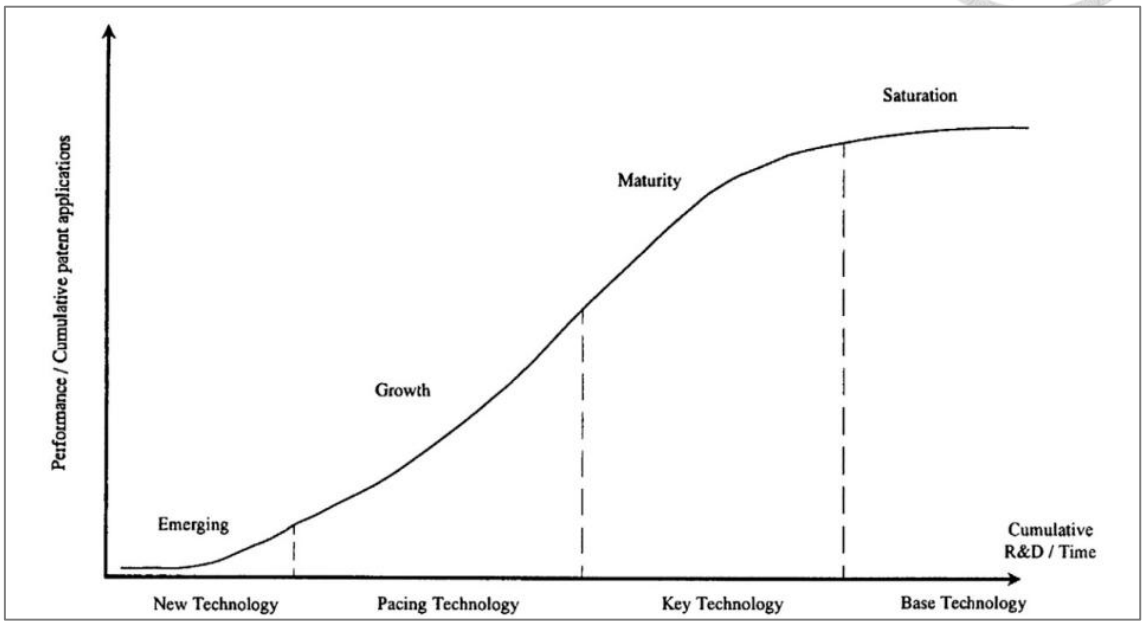

Figure 2-5

The S-Curve Concept of Technology Life Cycle.

Note. Reprinted with permission from "Technology life cycle analysis method based on patent documents" by Gao, L., Porter, A. L., Wang, J., Fang, S., Zhang, X., Ma, T., ... & Huang, L., 2013, "Technological Forecasting and Social Change", 80(3), 398-407 (https://doi.org/10.1016/j.techfore.2012.10.003). Copyright 2013 by Elsevier.

Patent indicators have been widely used to assess TLC stages, including application volume, citation patterns, and technological classifications (Gao et al., 2013). More recently, patent citation network analysis provides a dynamic lens for tracing technological communities and identifying inflection points in innovation trajectories (Huang et al., 2022).

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Building on this view, Dosi (1982) proposed the concepts of "technological paradigms" and "technological trajectories", framing technology development as both cumulative and path-dependent. A paradigm defines the cognitive boundaries and shared problem-solving approaches within a technological domain. Within that paradigm, trajectories represent iterative, directional progress along key performance dimensions. Technologies with strong trajectories exhibit predictable scaling, whereas those with weak trajectories face uncertainty in standardization and long-term planning.

Complementing Dosi's evolutionary logic, Anderson and Tushman (1990) introduced a cyclical model of technological change featuring "technological discontinuities" and the emergence of "dominant designs" (see **Figure 2-6**). Discontinuities initiate an "era of ferment" in which competing variations coexist, accompanied by market and technical uncertainty. Over time, a dominant design emerges, not necessarily at the technological frontier, but as a compromise shaped by user needs, production constraints, and regulatory compatibility. This dominant design becomes the foundation for diffusion, scaling, and industrial investment.

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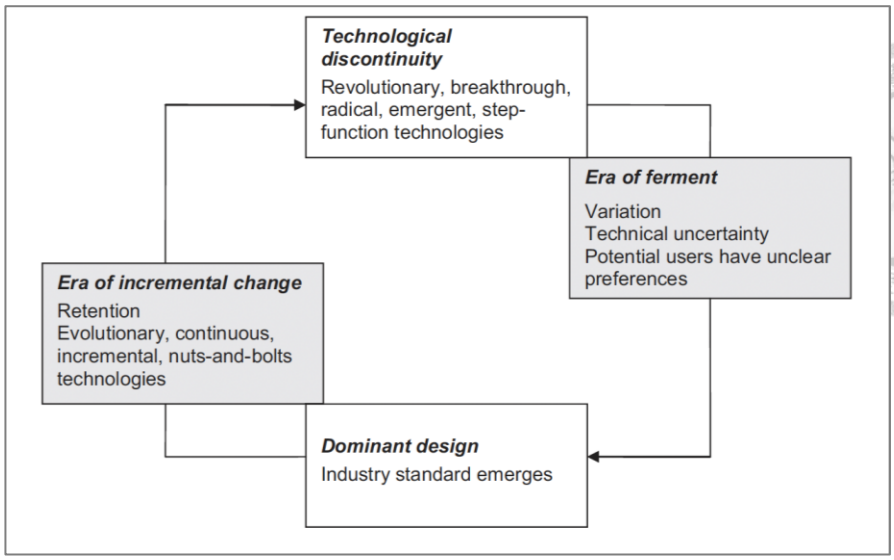

Figure 2-6

Macro Technology Life Cycle (Concepts of Technological Discontinuity and Dominant Design)

Note. Reprinted with permission from "The technology life cycle: Conceptualization and managerial implications" by Taylor, M., & Taylor, A. (2012), "International journal of production economics", 140(1), 541-553 (https://doi.org/10.1016/j.ijpe.2012.07.006). Copyright 2012 by Elsevier.

2.4.2 Organizational Capabilities and Strategic Positioning

Technological development is not only a function of performance metrics but also of organizational behavior. Firms navigate technological uncertainty through strategic positioning and capability building. The concept of "strategic groups" highlights that firms within an industry may cluster based on similar strategic orientations or mobility barriers (McGee & Thomas, 1986; Peteraf & Shanley, 1998). These clusters influence technology adoption rates, investment priorities, and competitive outcomes.

Technology forecasting (TF) enhances strategic decision-making even further. Among the various TF methods, patent analysis has emerged as a key quantitative

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approach for identifying emerging trends, mapping innovation networks, and informing R&D resource allocation (Cho & Daim, 2013; Kim & Bae, 2017). It supports anticipatory governance by reducing uncertainty and aligning internal capabilities with external trajectories.

2.4.3 Institutional Environment and Innovation Policy

Technological trajectories unfold within a broader socio-technical system, which includes users, regulators, infrastructure, and cultural norms (Geels, 2005). These heterogeneous elements co-evolve, and innovation often begins within protected niches, incubation environments where new technologies undergo iterative learning through use, interaction, and feedback. This niche accumulation process allows technologies to stabilize and build momentum before entering mainstream markets.

To support such transitions, effective innovation policy is crucial. Drawing on innovation system theory, technology development is increasingly viewed as a product of interactions among firms, universities, governments, and intermediary organizations (Borrás & Edquist, 2013). These systems function optimally when policies minimize fragmentation and facilitate knowledge sharing.

Policy instruments, categorized as regulatory, economic/financial, and soft instruments, play critical roles in shaping innovative outcomes. These tools may target the supply side (e.g., R&D subsidies, intellectual property regimes) or demand side (e.g., public procurement, outcome-based payments), influencing not only which technologies are developed but also how they scale and diffuse. (Edler & Georghiou, 2007). Designing a compelling policy mix requires attention to technology maturity, market uncertainty, and broader socio-economic objectives.

Taken together, these multi-level frameworks offer a comprehensive lens for

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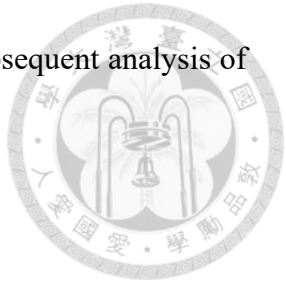
understanding and guiding the development, adoption, and institutionalization of emerging health technologies. They serve as a foundation for the subsequent analysis of CGT in this study.



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Chapter 3 Research Method

3.1 Study Design Overview

This study employs a mixed-methods research design using multiple quantitative and qualitative data sources, as illustrated in **Figure 3-1**.

- Quantitative data: including patent records, clinical trial registries, and CGT approval and pricing statistics—provides macro-level evidence of technological development trends and commercialization patterns, primarily addressing Research Question 1 (RQ1) and partially answering Research Question 2 (RQ2).
- Qualitative data: including expert interviews and international policy document analysis, offers critical contextual insights into regulatory structures, payment models, and system-level barriers.

By integrating comparative policy analysis and technology landscape analysis, the study explores interactions between payment systems, regulatory frameworks, and industrial dynamics that influence the emergence of CGTs. This triangulation approach not only identifies systemic bottlenecks and promising therapeutic modalities but also enables a comprehensive exploration of the research questions, particularly informing the strategic implications for Research Question 3 (RQ3).

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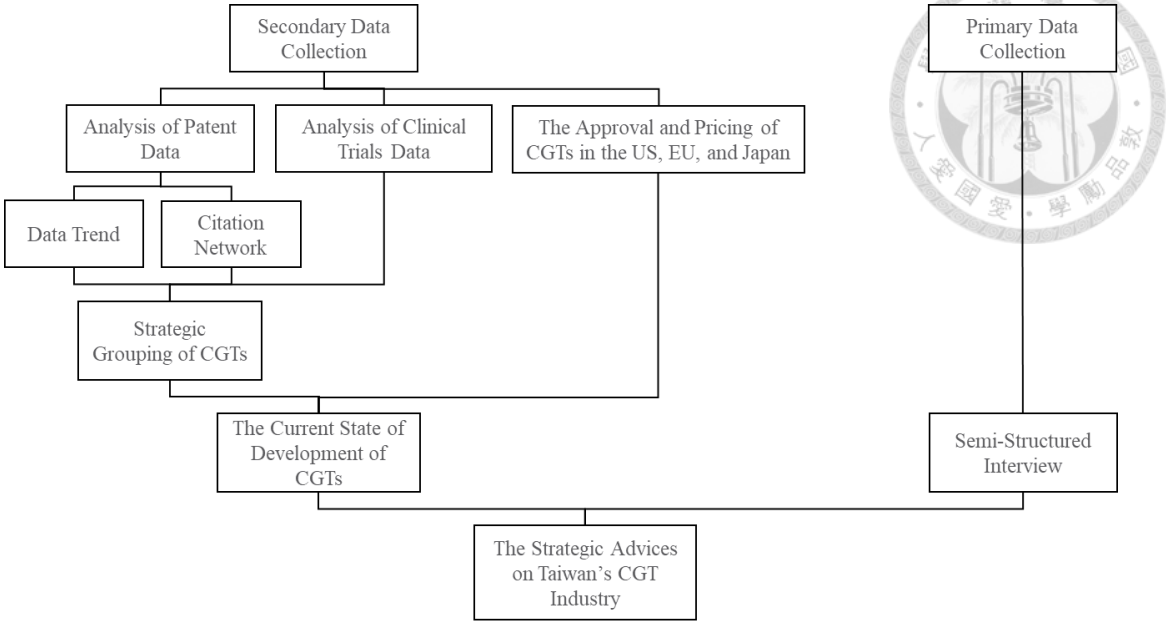

Figure 3-1

Research Design and Methodological Framework

Note. Compiled by the researcher. CGT=cell and gene therapy.

3.2 CGT Technology Landscape

Patents analysis and clinical trials analysis were adopted to understand the current technological development landscape of CGTs.

The six CGT modalities are chosen because they are among the main CGT developing modalities, and they have sufficient data from patents and clinical trials.

3.2.1 Patent Analysis

Data Collection and Search Strategy

The data employed in this study were downloaded from the Global Patent Search System (GPSS) provided by the Taiwan Intellectual Property Office (TIPO). The system includes more than 160 million patent data points from central patent offices (TIPO, 2025).

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To ensure data accuracy and consistency, the names published by TIPO were adopted as the standard reference. In instances where discrepancies arose between the names of multinational corporations or their subsidiaries as recorded by TIPO and those listed on Google Patents, the classification and statistical analysis in this study relied solely on the applicant information registered with TIPO.

The Boolean Search strategies and GPSS retrieval results for the six selected CGTs are displayed in **Table 3-1**. The latest date of the gathered data is December 31, 2024, and only US-issued patents are selected.

The data were collected and processed up to 2024, with a focus on analyzing the volume and trends of patent applications in key areas of CGT. By formalizing the database, the study ensures that the data structure is standardized, more transparent, and easier to manage, thereby enhancing data consistency and completeness.

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Table 3-1

Boolean Search Strategies and Global Patent Search System (GPSS) Retrieval Results for Selected Cell and Gene Therapy Technologies (as of December 31, 2024)

Category	Treatment	Boolean Search	Number of GPSS results
Gene Therapy Modality	AAV	(AAV) OR (adeno-associated virus)	27,992
	CAR-T	(CAR-T) OR (chimeric antigen receptor T cell)	4,855
	CRISPR	(CRISPR) OR (CRISPR-Cas9)	13,981
Cell Therapy Modality	MSC	(Mesenchymal stem cell*)	14,221
	NK Cell	(NK cell) OR (natural killer cell)	16,030
	iPSC	(iPSC) OR (induced pluripotent stem cell*)	7,769

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), retrieved on June 9, 2025. Boolean search queries were designed to identify relevant patents for each category. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

Patent Trend and Entity Analysis

The study tracks the number of patent filings per year to examine the growth trajectory of each technology. Additionally, the analysis examines the geographical distribution of primary applicants by country and their relative contribution to global patent activity. The top patenting countries and organizations are ranked and compared across the six selected technologies to identify regional innovation dominance, market orientation, and applicant diversity.

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Patent Citation Network Analysis

The following information is then selected from each patent and output into a text file: application date, issue date, application number, issue number, title, and citation. The technical analysis is conducted through social network analysis (SNA), treating each patent as a node and citations as links to reveal interaction patterns between technologies. Centrality, InDegree, and OutDegree metrics are used to identify key patents and understand their roles in controlling resources and shaping network influence (see **Table 3-2**). Citation pathways with over 50 bidirectional links are visualized to trace major technological trajectories.

Table 3-2

Main Indicators in Social Network Analysis

Indicator	InDegree Centrality	OutDegree Centrality	Betweenness Centrality
Definition	Number of patent *i* cited by other patents	Number of patent *i* cites other patents	Technological Intermediacy
Calculation	$d(i) = \sum_j m_{ji}$ Patent *j* cite (link) to patent *i*, m_{ji}=1	$d(i) = \sum_j m_{ij}$ Patent *i* cite (link) to patent *j*, m_{ij}=1	$b(i) = \sum_{j,k \neq 1} \frac{g_{jik}}{g_{jk}}$ g_{jk}: The shortest path between patens *j* and *k*; g_{jik}: The shortest path from patent *j* to paten *k* must pass through patent *i*

Note. Compiled by the researcher.

To enhance the analysis, artificial intelligence (AI) techniques, including network analysis algorithms and natural language processing (NLP), are applied using Gephi and external text mining tools. Central patents and clusters are detected through degree and betweenness centrality, while NLP helps interpret the thematic focus of each cluster. This integration of AI-supported analytics follows recent advancements in computational

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patent analysis for high-technology fields (Lee et al., 2018; Song et al., 2023). GPT-4 was used as a generative AI tool to assist in summarizing the content of clustered patent groups. All outputs were reviewed and revised by the author to ensure semantic accuracy.

Networks were visually analyzed to:

- Identify technology clusters and subfields;
- Highlight influential patents and organizations;
- Trace the development of technical pathways and their fragmentation or convergence.

3.2.2 Clinical Trials Analysis

Source and Criteria

Clinical trial data were retrieved from ClinicalTrials.gov on May 20, 2025, using the same keyword strategies as patent searches shown in **Table 3-1**. The data were collected and processed up to 2024, with a focus on analyzing the volume and trends of patent applications in key areas of CGT. By formalizing the database, the study ensures that the data structure is standardized, more transparent, and easier to manage, thereby enhancing data consistency and completeness.

Trials were categorized by therapy type, trial phase, and therapeutic area.

Therapy Indications and Trial Phase Distribution

The study classifies trials by therapeutic area (e.g., cancer, genetic, cardiovascular) and by trial stage (early-phase, phase I–IV). This helps evaluate the approximate stage of development of each technology towards clinical adoption.

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3.2.3 Strategic Grouping

A two-dimensional matrix was developed to map the six CGT modalities based on two variables: the technology development stages (indicating technological innovation) and the number of phase II+ trials (indicating clinical maturity). This quadrant framework allowed technologies to be categorized as nascent, transitional, established, or convergent.

The grouping results are presented and discussed in Chapter 4.

3.3 Comparative Analysis from a Regulatory Perspective

3.3.1 Country Selection and Data Sources

Three jurisdictions, the United States, the European Union, and Japan, were selected due to their regulatory maturity, market activity in CGT, and the availability of documentation. Policy data were collected from:

- Regulatory agency guidelines and official websites;
- Industry association white papers;
- Peer-reviewed literature.

3.3.2 Analytical Framework: Regulation and Payment

This study applies a structured comparative approach to examine CGT-related policies in terms of regulatory design and pricing mechanisms. Each country was analyzed along the following dimensions:

1. Regulatory Approval Pathways: Availability and characteristics of fast-track, conditional, or CGT-specific regulatory mechanisms;
2. Pricing and Value Assessment: Application of HTA processes, value-based pricing, and cost-effectiveness analysis;
3. Coverage Architecture: Role of public funding systems, reimbursement

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eligibility, and scope of inclusion;

3.4 Semi-Structured Expert Interviews

To enhance contextual understanding and validate analytical results, this study conducted semi-structured interviews with experts from industry, academia, and private insurance companies involved in the development and financing of CGTs in Taiwan. The interview design was informed by the study's analytical framework, focusing on regulatory pathways, pricing challenges, technical selection rationales, and industrial positioning.

The results and insights of the interviews will be incorporated into Section 0.

3.4.1 Interview Design and Scope

The interview guide for industrial experts was structured into four thematic sections: technology and clinical development, cost and payment mechanisms, policy and industrial environment, and forward-looking reflections (the full interview protocol is provided in Appendix A).

The interview for professionals from medical institutions focuses on the operational aspects of providing CGT and the execution situation.

The discussion with payment system-related experts will focus on their opinions and actions taken in response to the emerging CGTs in Taiwan.

3.4.2 Participant Selection and Process

Participants were selected using purposive sampling to reflect diverse perspectives across the CGT value chain, including:

- Executives or R&D heads of CGT-related biotech firms;

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- Professionals or physicians working at medical institutions who are familiar with regenerative medicine operations;
- Payment system-related experts include individuals from private insurance companies.

Interviews were conducted in Mandarin between June and July of 2025, and each session lasted approximately 45–60 minutes. Interview responses were anonymized and coded thematically. For confidentiality, citations in Chapter 4 refer to interviewees by assigned labels (e.g., Interviewee A, B, C) as shown in **Table 3-3**

Table 3-3

List of Interviewees

ID	Role	Sector	Area of Expertise
Interviewee A	Associate Marketing Director	CGT Company	Regulation, market strategy
Interviewee B	Director of Medical Affairs Office	Medical institute	Administration
Interviewee C	Senior Sales	Insurance Company	Insurance merchandise
Interviewee D	General Manager	CGT Company	Regulation, industry insight

Note. Compiled by the researcher.

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Chapter 4 Discussion and Results

The following section will be divided into three sub-sections:

4.1 The Development of CGT Modalities

4.2 The Landscape of CGT Approvals and Pricing: Case Study of the US, EU, and Japan

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CGTs in Taiwan

Figure 4-1 is a mind map presenting the thematic structure of Chapter 4 and highlights how the sections in Chapter 4 address the three leading questions proposed in Section 1.2 (RQ1-RQ3). The strategy recommendations will be concluded in Chapter 5.

4.1 The Development of CGT Modalities

Three gene therapies and three cell therapies are selected for further analysis: AAV, CAR-T, CRISPR, MSC, NK cell, and iPSC. Three aspects of the patent data are further compiled and analyzed in the section: yearly application number, countries of primary applicants, and a list of primary applicants.

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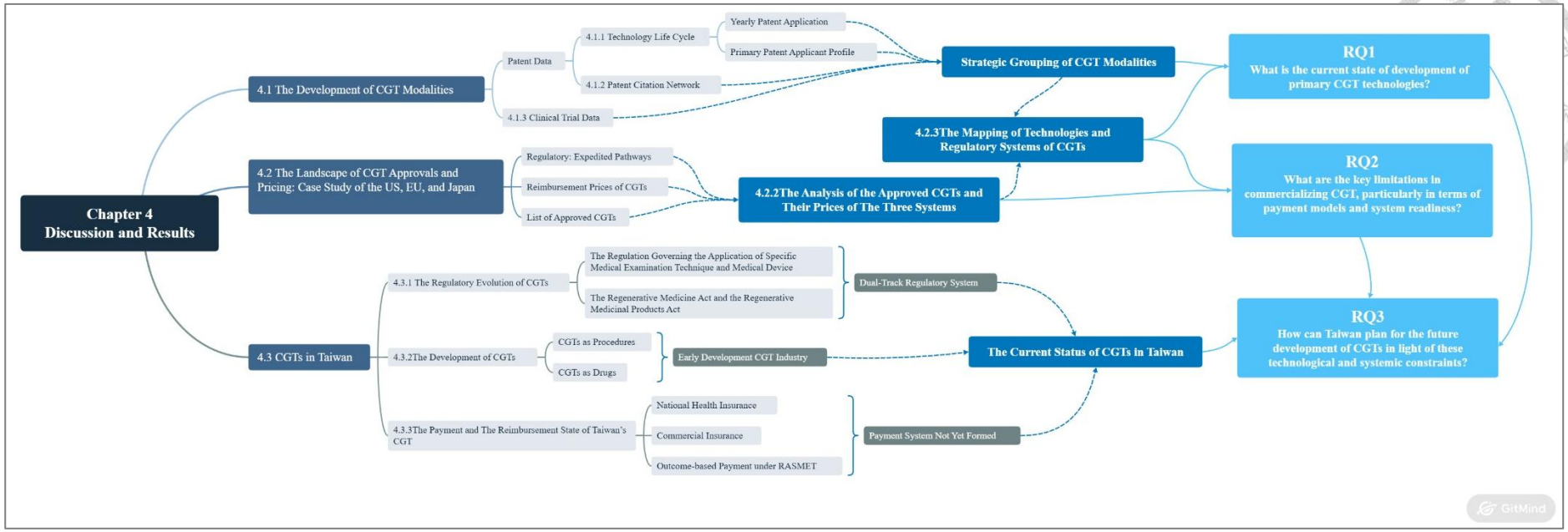

Figure 4-1

Overview of Chapter 4: Structure and its Correspondence with Research Questions

Note. Compiled by the researcher using GitMind. CGT=cell and gene therapy; RQ=research question.

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4.1.1 The Technology Life Cycle of CGTs

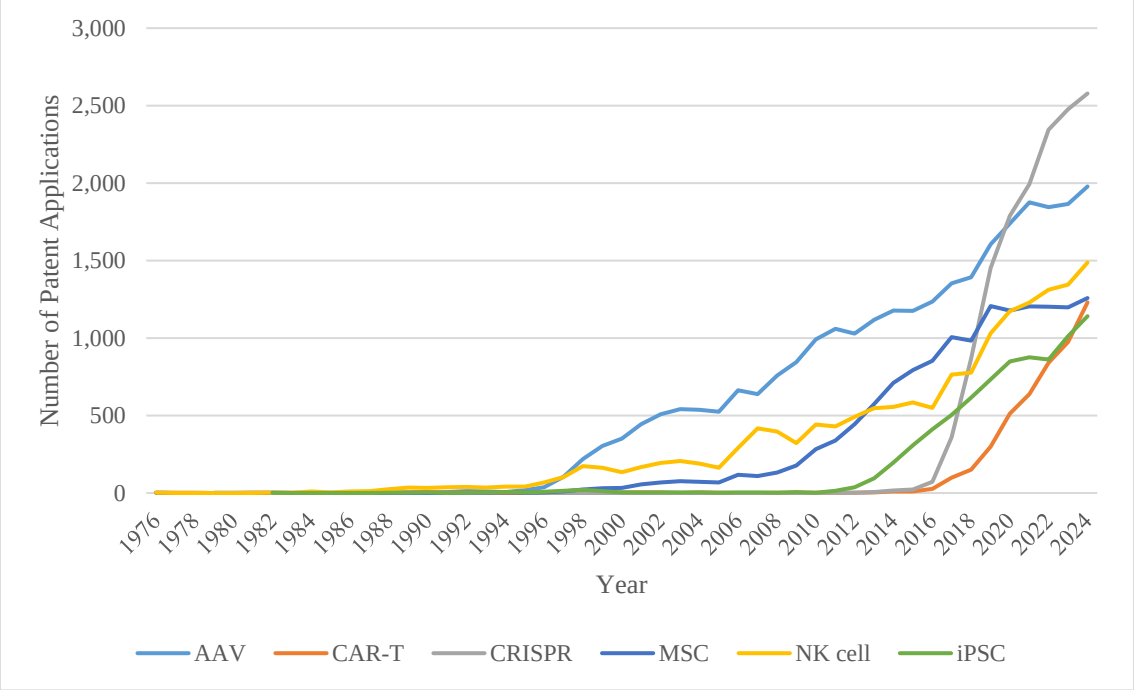

Figure 4-2

The Yearly Patent Applications of Cell and Gene Therapies (1976–2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

Figure 4-2 presents the yearly increments of the six. By applying the TLC framework with the compiled statistics, it reveals clear differentiation in the maturity stages of each technology.

While MSCs have long exhibited steady growth in patent filings, the rate of increase has noticeably reduced since 2019. The deceleration suggests that (MSCs of stem cell) technology may be transitioning from the late growth phase into early maturity, in line with the Technology Life Cycle model. However, unlike AAV, which has reached a more

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consolidated and standardized status, MSC applications remain diverse and fragmented, with fewer globally approved products. Thus, MSCs are best interpreted as a technology entering maturity, but not yet fully stabilized at the platform or commercial level.

AAV has long been considered a mature viral vector platform; its patent trajectory shows a more nuanced pattern. AAV displays the longest trajectory, with steady growth beginning in the late 1990s, followed by a plateauing trend post-2017. This pattern suggests that AAV has entered the mature phase of its lifecycle, with innovation stabilizing and incremental improvements dominating patent activity. However, after a steady rise and a mild dip in 2022, AAV-related filings increased again in 2024, suggesting a potential second wave of innovation. This may be driven by advancements in capsid engineering, novel payload design, or the expansion of clinical indications.

NK cell technologies appear to be in a growth phase, based on their long-standing presence and growing patent activity. However, their trajectory remains unstable, with fluctuations in annual filings and ongoing divergence in technical approaches. This suggests that NK therapies have yet to consolidate into a dominant design or clinical platform and remain in an exploratory state typical of technologies nearing—but not yet reaching—maturity.

iPSCs, emerging after 2006, display a smooth and relatively steady rise, indicating the growth phase, although they are likely approaching maturity as the rate of increase begins to level off after 2021.

In contrast, CAR-T and CRISPR therapies show distinctly different trajectories. CAR-T began to rise sharply around 2015, showing a steeper curve between 2017 and 2024. While CAR-T is a relatively recent innovation, its growth has accelerated rapidly, placing it in a late exponential growth phase, potentially transitioning toward maturity. CRISPR, on the other hand, exhibits the most striking pattern, with near-exponential

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growth starting from 2014, as its patent count surpasses 2,500 by 2024. This suggests that CRISPR remains in the high-growth phase, with innovation still expanding rapidly and far from saturation. However, its growth rate is starting to slow down, indicating a possible stage transition from growth to late growth.

From a TLC perspective, this comparative analysis reveals a multi-phase technological ecosystem within the CGT landscape: while some technologies (such as MSC and AAV) are stabilizing, others (like CRISPR and CAR-T) are aggressively advancing, signaling active knowledge creation and potential clinical translation ahead.

Table 4-1 and **Table 4-2** present the statistics for the countries of primary applicants for the patents of each CGT. The top 20 countries in each category of CGT remain largely consistent, with the United States ranking first, accounting for over 60% of primary applicants, excluding CAR-T and CRISPR, which are at 71.12% and 83.79%, respectively. Five of the twelve European countries are among the top 20 in all six therapies: France, Germany, the Netherlands, Switzerland, and the United Kingdom. Six out of eight Asian countries are on the list across all six therapy categories, too, including China, Japan, Korea, Israel, Singapore, and Taiwan. Hong Kong and India, as the other two Asian countries, only made it into the top 20 in CAR-T and MSC. Regarding North America and Oceania, Canada, the United States, and Australia are also included on the list of all six therapies. The Cayman Islands are listed for CAR-T, NK cells, and iPSCs, while New Zealand is listed for CRISPR only.

The distributions after the second place in each therapy are different. For gene therapies, the ranking of European countries is slightly better than that of Asian countries, as more European countries are represented in the top 10. In contrast, the situation is reversed in cell therapies, where Japan, Korea, and Israel are more frequently found in the top 10.

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The result might be biased because only US publications are considered; however, the high percentage still indicates that the United States has been recognized as an essential market for CGT companies.

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Table 4-1

Top 20 Statistical Ranking of Countries by the Primary Patent Applicant of the Selected Gene Therapies (as of December 31, 2024)

Rank	AAV			CAR-T			CRISPR		
	Country	Number	%	Country	Number	%	Country	Number	%
1	United States	17,433	68.72%	United States	3,428	71.12%	United States	7,519	83.79%
2	Germany	1,332	5.25%	Germany	249	5.17%	Switzerland	212	2.36%
3	Japan	1,012	3.99%	United Kingdom	233	4.83%	Japan	157	1.75%
4	France	750	2.96%	China	207	4.29%	France	154	1.72%
5	Canada	560	2.21%	Switzerland	130	2.70%	China	139	1.55%
6	Australia	524	2.07%	France	108	2.24%	United Kingdom	132	1.47%
7	United Kingdom	507	2.00%	Japan	80	1.66%	Netherlands	114	1.27%
8	Switzerland	481	1.90%	Korea	61	1.27%	Germany	113	1.26%
9	Korea	446	1.76%	Israel	47	0.98%	Canada	68	0.76%
10	Netherlands	312	1.23%	Canada	44	0.91%	Israel	67	0.75%
11	Belgium	310	1.22%	Singapore	37	0.77%	Korea	54	0.60%
12	China	309	1.22%	Cayman Islands	30	0.62%	Australia	37	0.41%
13	Israel	307	1.21%	Belgium	25	0.52%	Denmark	21	0.23%
14	Denmark	148	0.58%	Denmark	23	0.48%	Belgium	20	0.22%
15	Italy	139	0.55%	Australia	17	0.35%	Singapore	18	0.20%
16	Ireland	108	0.43%	Netherlands	17	0.35%	Sweden	18	0.20%
17	Taiwan	98	0.39%	Taiwan	15	0.31%	Taiwan	17	0.19%
18	Singapore	78	0.31%	Ireland	15	0.31%	Italy	15	0.17%
19	Sweden	65	0.26%	Hong Kong	7	0.15%	New Zealand	13	0.14%
20	Austria	65	0.26%	Austria	6	0.12%	Ireland	12	0.13%

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats.

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Table 4-2

Top 20 Statistical Ranking of Countries by the Primary Patent Applicant of the Selected Cell Therapies (as of December 31, 2024)

Rank	MSC			NK Cell			iPSC		
	Country	Number	%	Country	Number	%	Country	Number	%
1	United States	9,422	68.10%	United States	9896	67.63%	United States	5194	67.74%
2	Japan	913	6.60%	Japan	603	4.12%	Japan	700	9.13%
3	Korea	413	2.98%	Germany	527	3.60%	Korea	183	2.39%
4	Germany	395	2.85%	United Kingdom	442	3.02%	United Kingdom	181	2.36%
5	Israel	393	2.84%	France	356	2.43%	France	169	2.20%
6	Switzerland	307	2.22%	Canada	338	2.31%	Switzerland	159	2.07%
7	United Kingdom	200	1.45%	China	296	2.02%	Israel	137	1.79%
8	Canada	199	1.44%	Switzerland	277	1.89%	Germany	128	1.67%
9	Taiwan	167	1.21%	Israel	248	1.69%	Canada	126	1.64%
10	Singapore	160	1.16%	Netherlands	182	1.24%	China	95	1.24%
11	China	158	1.14%	Korea	175	1.20%	Sweden	85	1.11%
12	France	150	1.08%	Belgium	142	0.97%	Singapore	84	1.10%
13	Australia	126	0.91%	Ireland	137	0.94%	Netherlands	66	0.86%
14	Belgium	109	0.79%	Denmark	126	0.86%	Australia	57	0.74%
15	Italy	83	0.60%	Australia	120	0.82%	Taiwan	57	0.74%
16	Sweden	77	0.56%	Taiwan	110	0.75%	Denmark	28	0.37%
17	Netherlands	69	0.50%	Sweden	109	0.74%	Belgium	27	0.35%
18	Ireland	66	0.48%	Cayman Islands	77	0.53%	Italy	23	0.30%
19	Spain	66	0.48%	Singapore	75	0.51%	Spain	23	0.30%
20	India	45	0.33%	Italy	59	0.40%	Cayman Islands	18	0.23%

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025. MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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Table 4-3 and **Table 4-4** present the primary applicants for each therapy. Of the 120 companies listed in the tables, approximately 60% are repeated. A total of 66 non-repeated companies are listed, with 42 of them appearing only once in the primary applicants' list for each therapy.

The Leland Stanford Junior University and the University of California are found among the top 20 primary applicants in all six therapy categories. The University of Pennsylvania is found in five therapies except in the MSC category. The University of Texas System is also listed in five therapies, excluding CRISPR.

The applicants listed for four out of six therapies include Harvard College, the Broad Institute, Inc., and the General Hospital Corporation. Meanwhile, Bristol-Myers Squibb, the Dana-Farber Cancer Institute, Inc., Gilead Sciences, Inc., Immatics Biotechnologies GmbH, the Massachusetts Institute of Technology, Novartis AG, Regeneron Pharmaceuticals, Inc., and the US Secretary Department of Health and Human Services (HHS) are involved in three therapies.

Most of the applicants originate in the United States, with the rest coming from other countries, such as Kyoto University from Japan, Immatics Biotechnologies GmbH from Germany, and Novartis AG from Switzerland.

Based on the count of ownership, no single company dominates in any of the therapies. Although the top three companies account for more than a quarter of patents in CRISPR, these companies are focused on agriculture rather than biotechnology. Therefore, from the perspective of clinical application of CGTs, the field is still in a stage of contention and experimentation.

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Table 4-3

Top 20 Primary Patent Applicants of the Selected Gene Therapies (as of December 31, 2024)

Rank	AAV			CAR-T			CRISPR		
	Company	Number	%	Company	Number	%	Company	Number	%
1	Immatics Biotechnologies GmbH	624	2.23%	Immatics Biotechnologies GmbH	142	2.92%	Pioneer Hi-Bred International, Inc.	1,701	12.17%
2	The Regents of the University of California	583	2.08%	The Trustees of the University of Pennsylvania	115	2.37%	Monsanto Technology LLC	1611	11.52%
3	The Trustees of the University of Pennsylvania	409	1.46%	Gilead Sciences, Inc.	100	2.06%	M.S. Technologies, L.L.C.	616	4.41%
4	The United States of America, as represented by the Secretary, Department of Health and Human Services	394	1.41%	The United States of America, as represented by the Secretary, Department of Health and Human Services	66	1.36%	Seminis Vegetable Seeds, Inc.	314	2.25%
5	Board of Regents, The University of Texas System	318	1.14%	Xencor, Inc.	66	1.36%	The Regents of the University of California	285	2.04%
6	ZymoGenetics, Inc.	302	1.08%	Novartis AG	62	1.28%	10X Genomics, Inc.	213	1.52%
7	The Board of Trustees of the Leland Stanford Junior University	239	0.85%	The Broad Institute, Inc.	54	1.11%	President and Fellows of Harvard College	208	1.49%
8	Human Genome Sciences, Inc.	225	0.80%	The Regents of the University of California	52	1.07%	The Broad Institute, Inc.	168	1.20%
9	President and Fellows of Harvard College	207	0.74%	Memorial Sloan Kettering Cancer Center	50	1.03%	Agrigenetics, Inc.	163	1.17%

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Table 4-3 (continued)

Rank	AAV			CAR-T			CRISPR		
	Company	Number	%	Company	Number	%	Company	Number	%
10	The General Hospital Corporation	207	0.74%	Celgene Corporation	44	0.91%	Inscripta, Inc.	156	1.12%
11	ResMed Pty Ltd	193	0.69%	Dana-Farber Cancer Institute, Inc.	40	0.82%	Regeneron Pharmaceuticals, Inc.	131	0.94%
12	alnylam pharmaceuticals, INC.	189	0.68%	Cellectis	37	0.76%	Massachusetts Institute of Technology	126	0.90%
13	Genentech, Inc.	187	0.67%	The Board of Trustees of the Leland Stanford Junior University	37	0.76%	Gilead Sciences, Inc.	107	0.77%
14	University of Massachusetts	185	0.66%	Autolus Limited	35	0.72%	Syngenta Participations AG	97	0.69%
15	INSERM (Institut National De La Santé Et De La Recherche Médicale)	181	0.65%	Juno Therapeutics, Inc.	35	0.72%	The General Hospital Corporation	97	0.69%
16	Amgen Inc.	166	0.59%	Board of Regents, The University of Texas System	33	0.68%	The Board of Trustees of the Leland Stanford Junior University	90	0.64%
17	Dana-Farber Cancer Institute, Inc.	154	0.55%	Amgen Inc.	32	0.66%	HM.Clause, Inc.	81	0.58%
18	Agensys, INC.	153	0.55%	City of Hope	32	0.66%	Syngenta Crop Protection AG	74	0.53%
19	The Broad Institute, Inc.	144	0.51%	Lentigen Technology, Inc.	31	0.64%	The Trustees of The University of Pennsylvania	69	0.49%
20	Bristol-Myers Squibb Company	132	0.47%	Achillion Pharmaceuticals, Inc.	30	0.62%	Wisconsin Alumni Research Foundation	67	0.48%

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats.

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Table 4-4

Top 20 Primary Patent Applicants of the Selected Cell Therapies (as of December 31, 2024)

Rank	MSC			NK Cell			iPSC		
	Company	Number	%	Company	Number	%	Company	Number	%
1	The Regents of the University of California	242	1.70%	Genentech, Inc.	545	3.40%	The Regents of the University of California	268	3.45%
2	Warsaw Orthopedic, Inc.	187	1.31%	The United States of America, as represented by the Secretary, Department of Health and Human Services	188	1.17%	President and Fellows of Harvard College	181	2.33%
3	Immatics Biotechnologies GmbH	118	0.83%	The Regents of the University of California	183	1.14%	The Board of Trustees of the Leland Stanford Junior University	107	1.38%
4	The Board of Trustees of the Leland Stanford Junior University	115	0.81%	Human Genome Sciences, Inc.	161	1.00%	Wisconsin Alumni Research Foundation	93	1.20%
5	President and Fellows of Harvard College	113	0.79%	The Board of Trustees of the Leland Stanford Junior University	157	0.98%	The General Hospital Corporation	87	1.12%
6	DePuy Synthes Products, Inc.	96	0.68%	Bristol-Myers Squibb Company	148	0.92%	The Broad Institute, Inc.	79	1.02%
7	Samumed, LLC	95	0.67%	Board of Regents, The University of Texas System	141	0.88%	Kyoto University	78	1.00%
8	CorMatrix Cardiovascular, Inc.	78	0.55%	3M Innovative Properties Company	131	0.82%	Regeneron Pharmaceuticals, Inc.	62	0.80%
9	Massachusetts Institute of Technology	75	0.53%	The Trustees of the University of Pennsylvania	122	0.76%	Sangamo Therapeutics, Inc.	59	0.76%

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Table 4-4 (continued)

Rank	MSC			NK Cell			iPSC		
	Company	Number	%	Company	Number	%	Company	Number	%
10	The General Hospital Corporation	74	0.52%	Gilead Sciences, Inc.	117	0.73%	Sangamo BioSciences, Inc.	57	0.73%
11	ZymoGenetics, Inc.	68	0.48%	Celgene Corporation	103	0.64%	Factor Bioscience Inc.	55	0.71%
12	Biomet Sports Medicine, LLC	67	0.47%	Dana-Farber Cancer Institute, Inc.	100	0.62%	Cellectis	54	0.70%
13	Osiris Therapeutics, Inc.	65	0.46%	Regeneron Pharmaceuticals, Inc.	99	0.62%	Regents of the University of Minnesota	53	0.68%
14	Johns Hopkins University	64	0.45%	Xencor, Inc.	96	0.60%	Johns Hopkins University	52	0.67%
15	University of Pittsburgh—of the Commonwealth System of Higher Education	64	0.45%	Schering Corporation	93	0.58%	The Trustees of the University of Pennsylvania	51	0.66%
16	Board of Regents, The University of Texas System	62	0.44%	Hoffmann-La Roche Inc.	92	0.57%	Massachusetts Institute of Technology	50	0.64%
17	Boston Scientific Scimed, Inc.	60	0.42%	Amarin Pharmaceuticals Ireland Limited	91	0.57%	University of Massachusetts	50	0.64%
18	Kyoto University	60	0.42%	Incyte Corporation	91	0.57%	International Business Machines Corporation	49	0.63%
19	NOVARTIS AG	58	0.41%	Novartis AG	88	0.55%	Viacyte, Inc.	47	0.60%
20	LifeCell Corporation	56	0.39%	ZymoGenetics, Inc.	87	0.54%	Board of Regents, The University of Texas System	43	0.55%

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025. MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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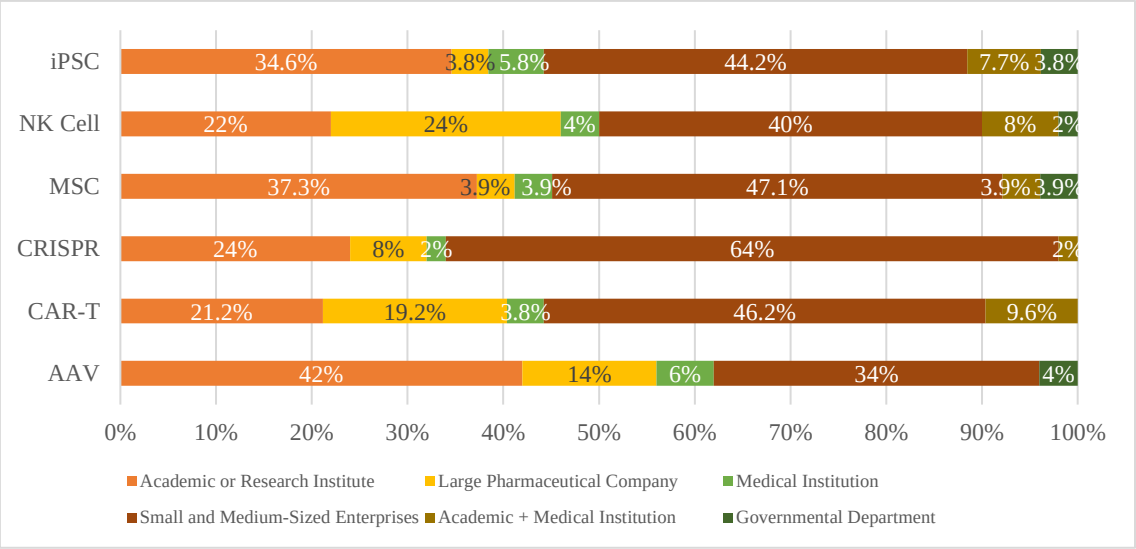

Figure 4-3

Distribution of Top 50 Patent Applicants by Organization Type (1976-2024)

Note. Data compiled by the researcher. Each technology includes the top 50 applicants (n = 50). "Large Pharmaceutical Company" is defined as a company listed in the Top 100 Sales Rankings in 2024 (CITELINE, 2025). AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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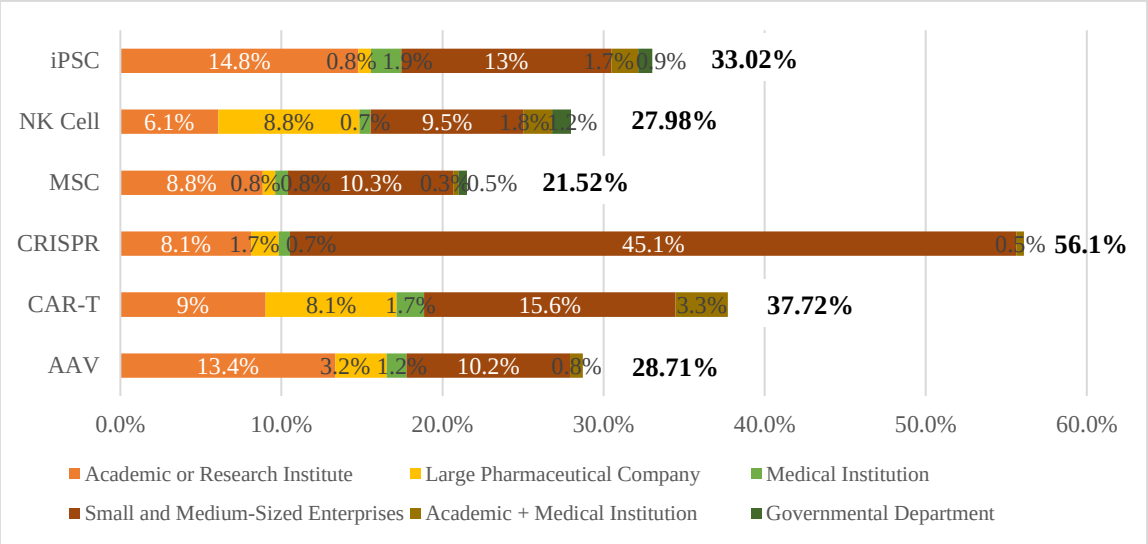

Figure 4-4

Share of Total Patents Held by Top 50 Applicants, by Organization Type (1976-2024)

Note. Data compiled by the researcher. Each technology includes the top 50 applicants (n = 50). "Large Pharmaceutical Company" is defined as a company listed in the Top 100 Sales Rankings in 2024 (CITELINE, 2025). AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

To further understand the innovation landscape of CGT technologies, the organizational composition and patent output of the top 50 patent applicants in each modality are examined, as shown in **Figure 4-3** and **Figure 4-4**. Two complementary dimensions were analyzed: the number of distinct applicants per category (e.g., academic, small and medium-sized enterprises (SMEs), big pharmaceutical companies), and the aggregate number of patents held by each category. The first reveals who participates in the innovation process; the second, who dominates in terms of patent volume.

Academic institutions and government agencies serve as the primary drivers during

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the early stages of basic research and initial technological exploration (Calleja-Sanz et al., 2020; Cho & Daim, 2013; Gao et al., 2013). As technology matures and its commercial potential becomes evident, the leading role gradually shifts to industry actors, including both startups and established companies (Cho & Daim, 2013; Gao et al., 2013). Thus, identifying the distribution of patent applicants in each category also provides an indicator for analyzing the stages of each modality located in TLC.

Figure 4-3 shows that small companies constitute the largest proportion of applicants in nearly all CGT modalities, especially CRISPR (64%) and MSC (47.1%), highlighting the role of start-ups and SMEs as early movers in these fields. Academic institutions remain consistent contributors, particularly in AAV and iPSC, where they comprise over one-third of all top applicants. Conversely, the number of big pharmaceutical companies remains relatively low in terms of applicant count, often below 10%, with slightly higher shares in CAR-T and NK Cell technologies.

Figure 4-4 focuses on the share of total patents held by each category, revealing more concentrated patterns of technological control. While academic entities frequently appear as applicants, they do not always dominate in terms of patent volume. In CRISPR, for example, small companies account for over 45% of all patents. In comparison, academic institutions contribute only 8.6%, illustrating a start-up–led consolidation of intellectual property (even if the top 3 applicants' data are ruled out since they are not related to medical implementation, the percentage of small companies of CRISPR drops to 17%, which is still slightly higher than the academic applicants). In contrast, AAV and iPSC exhibit a more proportional alignment between applicant count and patent holdings within academia, reflecting a sustained academic ownership model.

CAR-T and NK Cell stand out as hybrid modalities where multiple organizational types contribute significantly to total patent volume, including academic-medical hybrids

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and Big Pharma. These findings indicate a translational innovation pattern, where clinical validation, commercialization, and basic research co-evolve. Overall, the divergence between who participates and who holds most patents highlights the power asymmetry within CGT innovation, providing a basis for understanding how different technologies evolve and transition into industrial adoption.

Table 4-5

Comparative Technology Life Cycle Stage Assessment of Selected Cell and Gene Therapy (CGT) Modalities

	Yearly Increments	Geographic concentration of applicants	Top 50 Primary Applicants Profile
AAV	Early Maturity (possible 2nd wave of innovation)	High (US, EU)	Academic > SMEs
CAR-T	Growth	High (US, EU)	SMEs > Academic > Large pharmaceutical companies
CRISPR	Growth to Late Growth	High (US, EU)	SMEs > Academics
MSC	Maturity	High (US, Asia)	SMEs > Academics
NK Cell	Late Growth to Early Maturity	High (US, Asia)	SMEs > Large pharmaceutical companies > Academics
iPSC	Growth	Very high (US, Asia)	Academics > SMEs

Note. SMEs=small and medium-sized enterprises. Compiled by the researcher. None of the selected CGTs exhibit sufficient long-term decline or technology obsolescence to be classified as "saturation" or "decline" under the TLC framework. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

Table 4-5 offers a comparative view of the six selected CGT modalities through the

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lens of the Technology Life Cycle (TLC) framework, cross-analyzed with the geographic concentration and institutional composition of their top 50 primary patent applicants. The results show clear differentiation in technological maturity and actor configurations across modalities.

Taken together, the applicant structure of CGT patents reveals how innovative ecosystems differ by platform. CRISPR demonstrates a highly concentrated, start–up–driven model, where a small number of SMEs dominate not only participation but also patent ownership, reflecting rapid commercialization and IP consolidation. The dominance of small companies in CRISPR patenting stems from its early applications in agriculture and microbial engineering, where development was rapid and regulatory barriers were low. This allowed SMEs to take the lead, while larger firms remained cautious due to ethical and legal uncertainties. Early patents controlled by academic spin-offs (e.g., CRISPR Therapeutics, Editas Medicine, etc.) also shaped a licensing landscape centered on small firms. The platform's modular, target-specific nature further suited the agility of start-ups over the scale of large pharmaceutical companies.

In contrast, AAV and iPSC maintain a strong academic footprint, with research institutions holding a majority of patents and forming the backbone of innovation efforts. These modalities exhibit less engagement from commercial sectors, indicating that technologies are academically mature but still awaiting broader industrial adoption. MSC, while more commercially dispersed, lacks dominance by any single stakeholder type, suggesting a fragmented innovation system, possibly due to regional regulatory diversity or heterogeneous clinical applications.

Lastly, CAR-T and NK cell therapies represent translationally mature CGT modalities that are actively advancing toward clinical adoption. In both cases, patent ownership is distributed among small companies, large pharmaceutical companies,

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academic institutions, and a notable presence of academic-medical hybrids. This diversified landscape reflects a collaborative ecosystem where translational research, clinical validation, and commercial deployment co-evolve. While small enterprises maintain a significant share of both applicants and patent volume, the involvement of large pharmaceutical firms and hybrid medical institutions suggests active bridging between research and the market. Such structures are indicative of technologies that are not only scientifically validated but also entering stages of industrial integration, often supported by hospital-based clinical trials and licensing partnerships.

By comparing organizational types with patent volume distribution, not only the structural dynamics of innovation but also the differential pathways by which CGT technologies evolve are observed. This structural asymmetry between "who participates" and "who controls" intellectual property underscores the varied maturity trajectories across the CGT landscape.

4.1.2 Patent Citation Network Analysis

The patent citation network results for each therapy are presented in the following section. Each has demonstrated different patterns and focuses.

Due to the large number of patents comprising a cluster, typically only patents with high centrality or high betweenness are investigated and analyzed. However, there is still a chance that the patents being searched are not representative enough for understanding the patent cluster. Thus, to enhance the interpretability of the cluster's thematic direction, GPT-4 was used to generate concise topic labels and summaries based on the titles of the clustered patents (see **Table B 3** in Appendix B).

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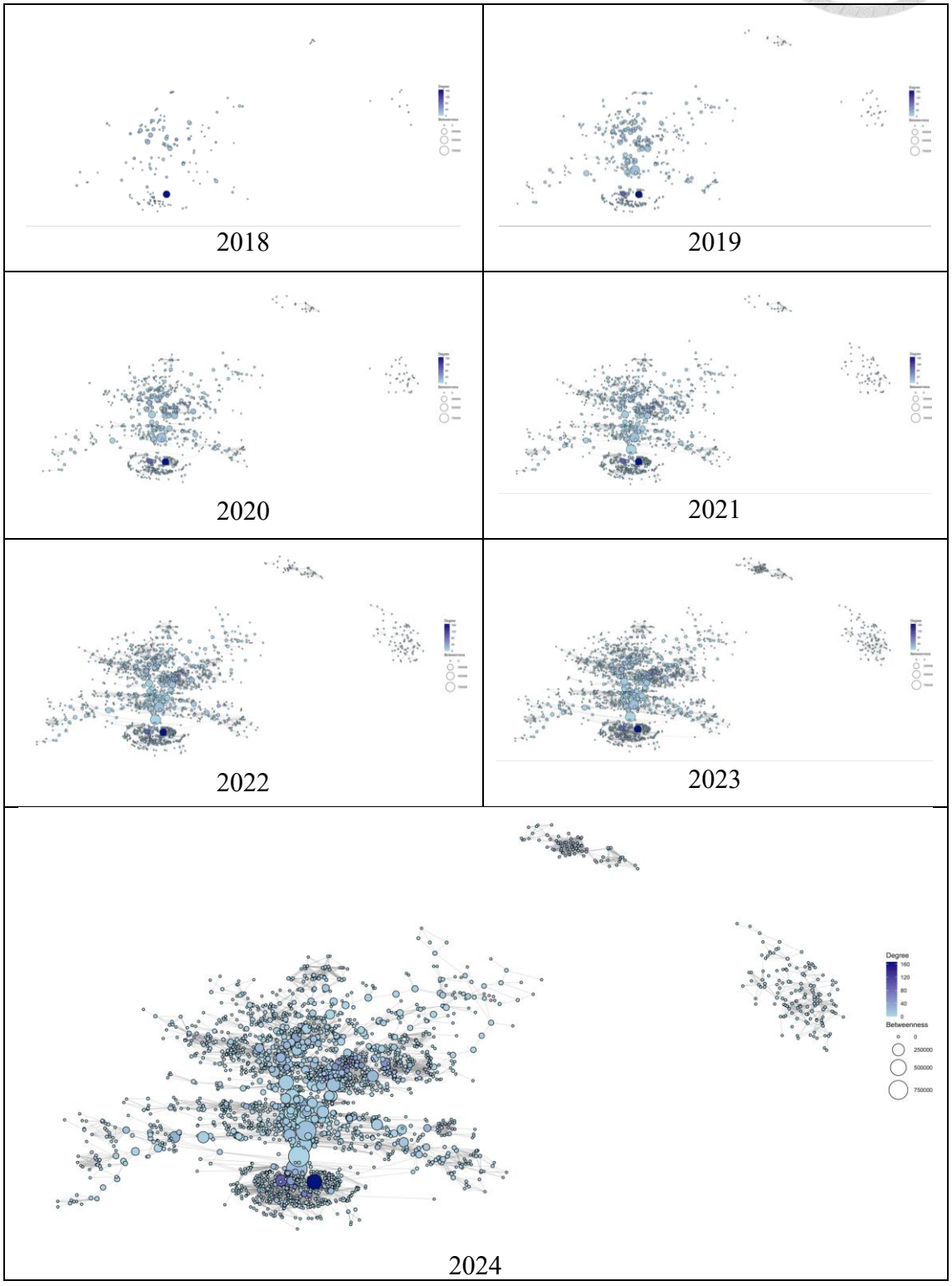
AAV

Table 4-6

The Patent Citation Network of Adeno-Associated Virus (AAV) by Year (2018-2024)



Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

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The patent citation network of AAV has formed three clusters in the past decade. The three clusters are not connected, and their extents of centrality and citation amounts also differ from one another.

As shown in **Table 4-6**, a highly centralized patent could already be found within the network. However, its impact did not extend beyond the cluster in 2018. The rough structure of the currently observed three clusters was established after 2019. The technology pathway continued to evolve, especially for the loser left corner one (Cluster (a)), which has a distinctive centrality on a particular patent and seems to have developed a technology pathway. Meanwhile, the top cluster finally obtained the missing piece and transformed into a cluster with a technology trajectory in 2023. As for the lower right cluster, no major cited patent has been found, and it remains dispersed and isolated from the other two clusters.

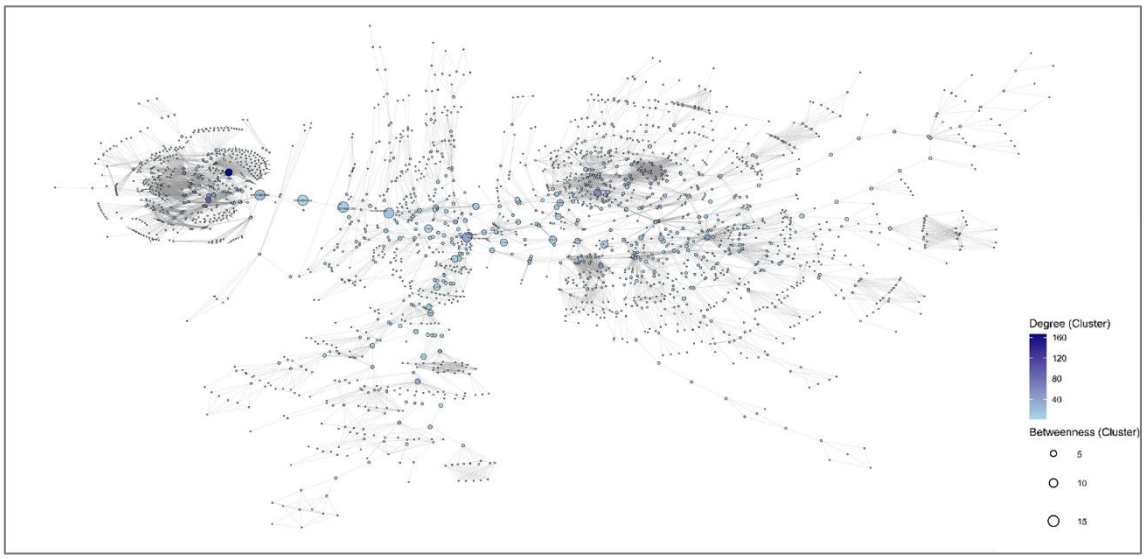

Figure 4-5

Cluster (a) of Adeno-Associated Virus (AAV) Patent Citation Network (1979-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

A few vague pathways can be found inside cluster (a), but none have yet become

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dominant. One pathway, composed of a few large patent nodes, connects the left part and the middle part, extending to the right part.

The pathway starts with patent NO. US10071148B2, which is centered on a condensed network. The next big patent node in this pathway is NO. US12168044B2 shares the same assignee and similar patent claims with the previous patent. They are both held by the German company Immatics Biotechnologies GmbH and describe inventions that include peptides, nucleic acids, and cells for use in immunotherapy against several types of cancer, such as lung cancer and non-small cell lung cancer (Weinschenk, Schoor, et al., 2024; Weinschenk, Walter, et al., 2018).

The subsequent three consecutive patents, NO. US11028142B2, NO. US11965012B2, and NO. US10442849B2, all titled “Compositions and methods for TCR reprogramming using fusion proteins”, are all held by TCR2 Therapeutics Inc. (Baeuerle et al., 2019, 2021, 2024). The US company was reported to have formed a strategic alliance with Adaptimmune to establish a leading cell therapy company focused on solid tumors (Adaptimmune, 2023).

From NO. US10442849B2, the pathway enters a network and diverges into two directions, but both are eventually connected to the upper right part of the cluster (a). The top branch starts with NO. US12037407B2, a patent applied for by Arsenal Biosciences Inc., provides recombinant nucleic acids encoding chimeric priming receptors targeting ALPG/P, chimeric antigen receptors recognizing MSLN, and shRNAs targeting FAS, PTPN2, and/or TOX, as well as cells and systems expressing these components and their methods of use (Williams et al., 2024). Afterward, the patent is followed by two patents related to gene editing. NO. US11497773B2, which is held by CRISPR Therapeutics AG and describes genetically engineered T cells with improved functionality and persistence (Dequeant et al., 2022). NO. US11111493B2, which KSQ Therapeutics Inc. holds,

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presents gene-regulating methods for immunotherapy (Benson et al., 2021).

The bottom branch begins with NO. US11254912B2, a patent application filed by CRISPR Therapeutics AG, which utilizes genetically engineered immune cells for cancer treatment, where CRISPR technology may be employed (Terrett et al., 2022). This branch then merges with another pathway that developed from the lower part of the cluster vertically at NO. US11661459B2. Century Therapeutics Inc. applies NO. US11661459B2 and includes polynucleotides encoding inactivated cell surface receptors, genetically engineered iPSCs, and derivative cells expressing CAR (Naso et al., 2023). The second sub-pathway developed from the lower part is formed by a series of patents surrounding tumor-associated antigens or immune-activating molecules. For example, NO. US10519248B2 is about HER2 and CD3 (Cheung et al., 2019), NO. US10696723B2 discloses activatable interleukin 12 polypeptides (Winston et al., 2020), and NO. US12065478B2 presents binding molecules targeting HER2 (Ferrara Koller et al., 2024).

The top right network has not yet developed an obvious center, but NO. US11866726B2 is observed to occupy a relatively important position in this part of the cluster. The patent describes genome editing systems and methods that allow for the detection and quantitative evaluation of all potential on-target gene editing outcomes, including targeted integration (Cotta-Ramusino & Margulies, 2024).

To summarize, the main patents identified in cluster (a) reveal a prominent yet emerging technical trajectory characterized by immunotherapeutic approaches that involve engineered immune cells, antigen-targeting receptors, and advanced gene-editing techniques. Core inventions within this cluster, represented by patents from companies such as Immatics Biotechnologies, TCR2 Therapeutics, CRISPR Therapeutics, and Arsenal Biosciences, converge to enhance T-cell therapies and refine the efficacy and precision of genome editing, highlighting their significant potential in next-generation

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cancer treatments.

The label provided by GPT-4 is more concise: CAR-T Cell Therapies with Gene Editing and Target Modulation", giving a more general understanding of the theme of the cluster.

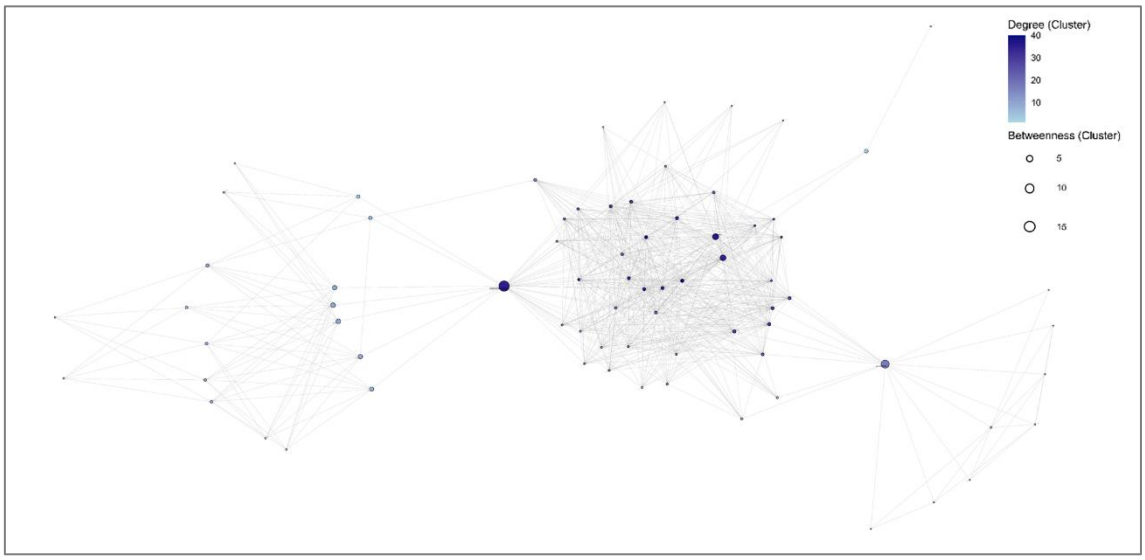

Figure 4-6

Cluster (b) of Adeno-Associated Virus (AAV) Patent Citation Network (1979-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

The structure of Cluster (b) is like a dumbbell, with the intertwined position happening to one single patent node, patent NO. US10246752B2. The patent was applied for by Adaptive Biotechnologies Corp., describing an improved method using DNA sequencing to identify personalized biomarkers in autoimmune patients or other conditions (Faham & Willis, 2019). The citation density is higher on the right side of the dumbbell, and each has similar betweenness, except for NO. US11613773B2 and NO. US11739372B2. Both patents were held by 10X Genomics Sweden AB and Illumina Inc., describing methods for spatially tagging nucleic acids in biological specimens using randomly located nucleic acid probes with unique barcode sequences, which enable

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multiplexed, spatially resolved nucleic acid analysis (Frisen et al., 2023a, 2023b).

NO. US10495554B2 then extends the right side and forms another loose network. The patent was applied for by Leland Stanford Junior University, which ranked No. 8 among the primary applicants, providing methods for preparing biological specimens for imaging analysis using microscopy (Deisseroth et al., 2019).

Cluster (b) is labeled “spatial omics and immune profiling technology” by GPT-4. The emergence of spatial transcriptomics, tissue imaging, and biomarker-guided analysis in the cluster (b) reflects a growing emphasis on downstream clinical application, where these enabling technologies play critical roles in validating, personalizing, and optimizing AAV-mediated gene therapy rather than constructing the AAV vector itself.

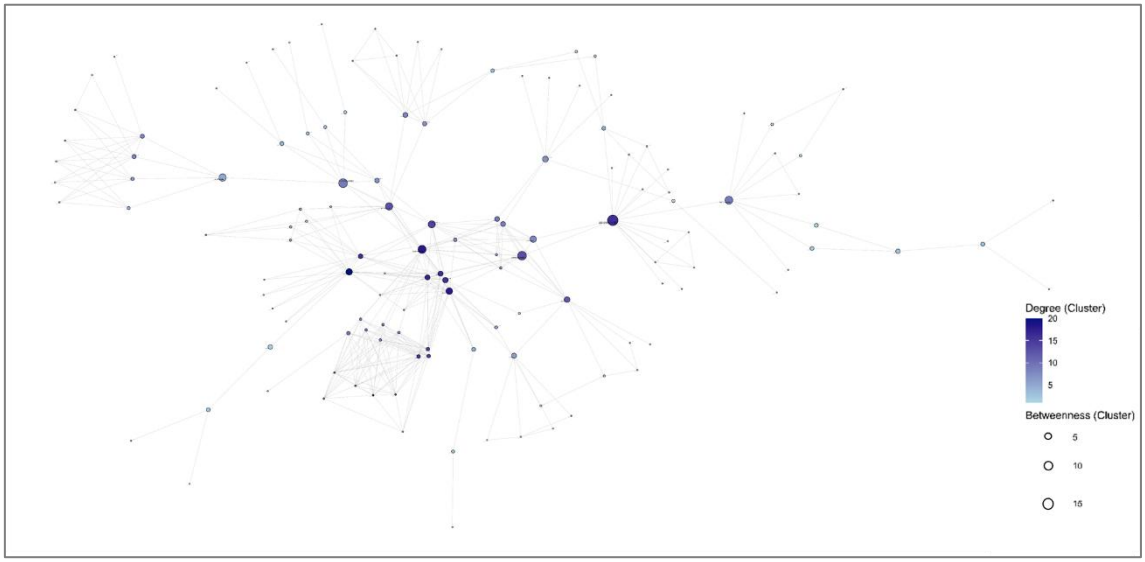

Figure 4-7

Cluster (c) of Adeno-Associated Virus (AAV) Patent Citation Network (1979-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (c) does not yet exhibit a well-defined internal structure; however, its thematic coherence is apparent, centering around RNA technologies and vaccine-related

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inventions, which also matches the label given by GPT-4.

Central to the cluster is NO. US10064959B2, held by ModernaTx Inc., which discloses modified nucleosides, nucleotides, and their applications (Schrum et al., 2018). Surrounding this node are additional Moderna patents related to RNA vaccines (Ciaramella & Himansu, 2018, 2020; Ciaramella et al., 2018).

At the periphery, NO. US10232055B2, assigned to the University of Pennsylvania, presents modified RNA molecules incorporating pseudo-uridine for therapeutic delivery with reduced immunogenicity (Kariko & Weissman, 2019).

Toward the lower right of NO. US10064959B2, a group of coronavirus vaccine-related patents by BioNTech SE and an actuator-related patent from Worcester Polytechnic Institute are observed (Muik et al., 2024; Popovic et al., 2024; Sahin et al., 2023, 2024). This sub-network extends via NO. US11241493B2 and NO. US12161711B2, both assigned to CureVac SE, which cover vaccines against the coronavirus and the Lassa virus, respectively (JASNY & Petsch, 2024; RAUCH et al., 2022).

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Table 4-7

Summary for Clusters of Adeno-Associated Virus (AAV) Patent Citation Network (1979-2024)

Cluster	No. of Patents	Technology Trajectory	GPT-4 Generated Label	Important Patents
(a)	2,340	Yes	CAR-T Cell Therapies with Gene Editing and Target Modulation	US10071148B2* US12168044B2** US11028142B2** US11965012B2** US10442849B2**
(b)	74	No	Spatial Omics and Immune Profiling Technologies	US10246752B2***
(c)	133	No	mRNA Vaccines and Delivery Platforms for Infectious Diseases	US12133899B2* US10064934B2* US10064959B2*** US12161711B2***

Note. Data compiled by the researcher. * represents a high degree in centrality; ** represents a high degree in betweenness; *** represents a high degree in both.

In sum, the AAV citation landscape reveals evolving yet disconnected innovation tracks: immunotherapy and gene editing from cluster (a), clinical analysis platforms from cluster (b), and mRNA therapeutics from cluster (c), each reflecting AAV's diverse and interdisciplinary developmental potential.

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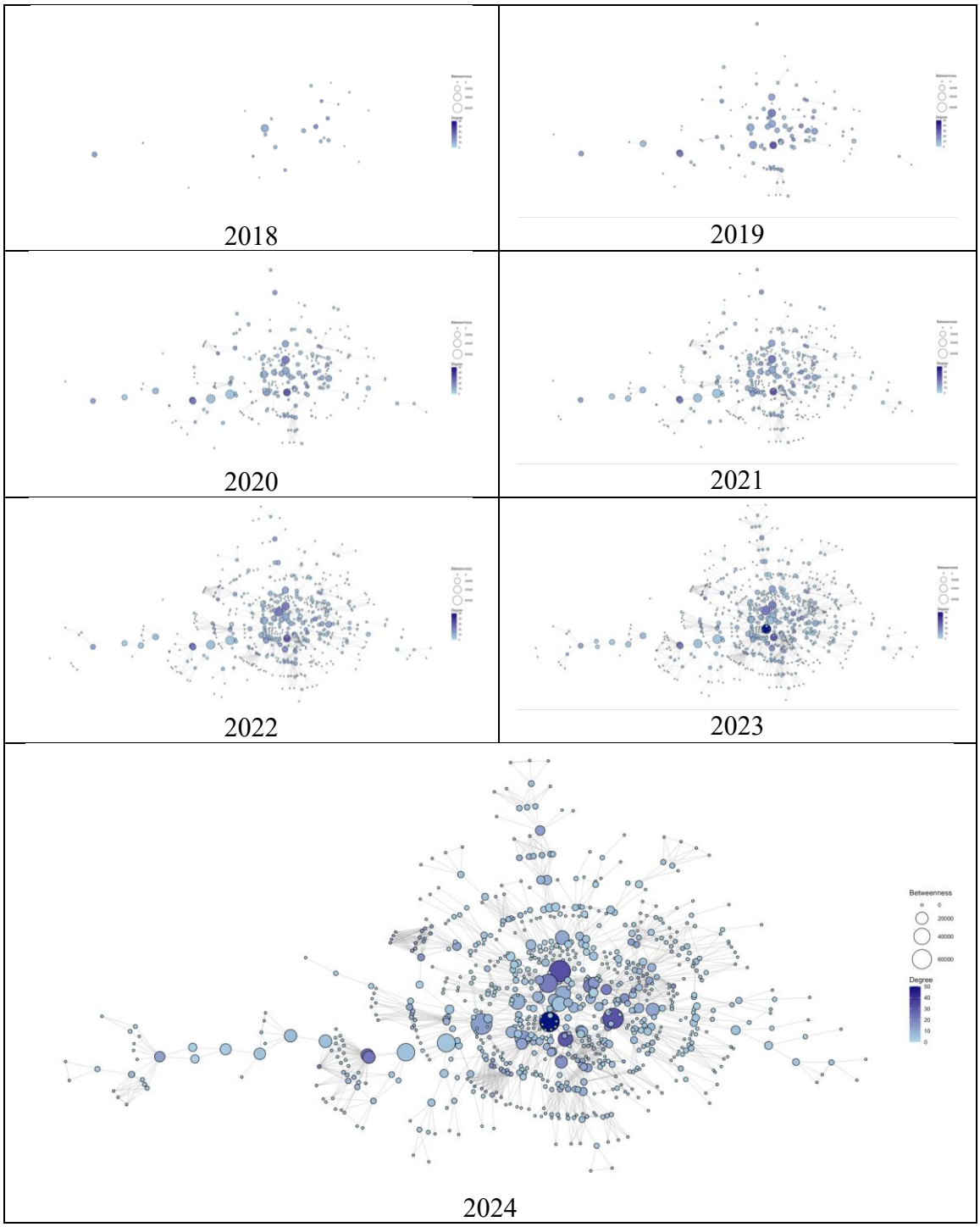
CAR-T

Table 4-8

The Patent Citation Network of Chimeric Antigen Receptor T Cell (CAR-T) by Year (2018-2024)



Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

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As shown in **Table 4-8**, since 2020, the developers in the field of CAR-T have been trying hard to “connect the dots”. Eventually, in 2024, it fully manifested its appearance and turned itself from fragmented clusters into a network with a clear technology trajectory.

The left side is in the early stages of technological development. Gradually, more patents emerged in the central part, and the significance of certain patents also increased.

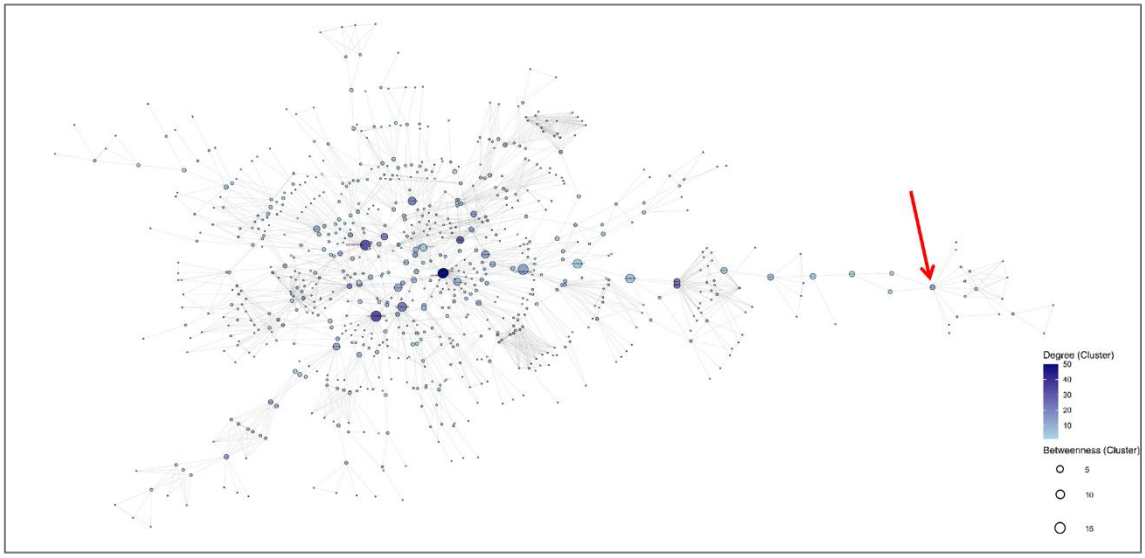

Figure 4-8

Cluster (d) of Chimeric Antigen Receptor T Cell (CAR-T) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

The patent citation network of CAR-T can be divided into two sections. One is that a single pathway was formed, but few surrounding patents were found or invented. The other section is the large network on the left side of the cluster, indicating that CAR-T has evolved to a more mature stage, and certain patents are now playing a significant role in the technology's development thereafter.

From the right side, the trajectory is composed of the following patents:

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- NO. US10100129B2 (marked with an arrow in **Figure 4-8**), which presents antibodies against CD73 by Bristol Myers Squibb Co. (Lonberg et al., 2018).
- The trajectory is then followed by a series of antibodies applied by Agenus Inc., Laboratoires Servier SAS, and I Mab Biopharma Co., Ltd. (Desjarlais et al., 2024; L. Fang et al., 2019; Grandal et al., 2023; Moore, Desjarlais, & Chu, 2019; Moore, Desjarlais, Chu, et al., 2019; Wang et al., 2020; Wang et al., 2021; Wilson et al., 2023).
- Some protein-related patents were added to the trajectory, such as heterodimeric proteins disclosed in NO. US10858417B2 and bispecific heterodimeric fusion proteins disclosed in NO. US10550185B2 by Xencor Inc. (Bernett et al., 2020; Moore et al., 2020), and methods for the regulated and controlled expression of proteins invented by Consulting Biochemist LLC, Obsidian Therapeutics Inc. (Suri et al., 2024). Xencor is ranked 5th among the primary applicants for CAR-T patents.
- The next node on this patent trajectory is the method of making CARs developed by the University of Texas System (Cooper et al., 2018), which ranked 16th.
- The trajectory is then linked to a double core, which is also now the most centralized patent in the entire CAR-T cluster. From here, the trajectory enters the network structure, and multiple pathways link the trajectory to the double core. For example, NO. US10428305B2, a larger node on the top, describes modified NK cells that express IL15 by the National University of Singapore and St. Jude Children's Research Hospital (Campana et al., 2019).
- The two patents that constitute the double core are all held by Century Therapeutics Inc., No. US11661459B2 is also found in the cluster of AAV and

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NK cells. NO. US11883432B2 discloses CARs that have adaptable receptor specificity (arCARs) (Carton et al., 2024). Till then, the formation of the CAR-T technology trajectory is complete.

Surrounding the double core, there are some noticeable patents due to their position on the network. One of them is NO. US10166255B2, which describes intracellular genomic transplant and methods of therapy. Its application was jointly filed by Intima Bioscience Inc., the University of Minnesota System, and the US HHS (Moriarity et al., 2019). According to statistics compiled by the researcher, Intima is one of the top 1,000 patent primary applicants. The University of Minnesota System is ranked 37th, and the US HHS is ranked fourth. NO. US10189903B2, on the other hand, is a patent held by Seattle Children's Hospital, which discloses the application of bispecific CARs in cancer treatment (Jensen, 2019). Seattle Children's Hospital is ranked 24th in the primary applicants, holding 29 patents in the dataset.

Around the double core, three directions have higher betweenness nodes than the others, indicating the possibility of becoming a sub-core or the future development of CAR-T.

- One direction is NO. US12144827B2 and NO. US11458167B2, which discloses different kinds of modified CARs, such as targeting ROR1-binding protein and engineered bi-specific CAR-T (Jensen, 2022; S. PARK et al., 2024).
- The second direction is RNA-related invention, led by Arsenal Biosciences Inc.'s patent NO. US12037407B2, which included shRNA and other designs to improve the clinical performance of CAR-T treatment (Williams et al., 2024).
- The third direction is NO. US10174095B2, providing compositions and

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methods for treating diseases associated with the expression of BCMA (Brogdon et al., 2019). Novartis AG and the University of Pennsylvania have applied for NO. US10174095B2. This group had also applied for NO. US12162922B2, the patent that links to NO. US10174095B2 and NO. US12037407B2 together, introducing T cells comprising an enhancer of T cell priming and CAR (Zhao et al., 2024). The group is ranked 6th and 2nd among the primary applicants.

Table 4-9

Summary for Cluster of Chimeric Antigen Receptor T Cell (CAR-T) Patent Citation Network (1976-2024)

Cluster	No. of Patents	Technology Trajectory	GPT-4 Generated Label	Important Patents
(d)	809	Yes	CAR-T and Engineered Immune Cell Therapies	US11661459B2* US11883432B2*

Note. Data compiled by the researcher. * represents a high degree in centrality; ** represents a high degree in betweenness; *** represents a high degree in both.

Interestingly, despite ranking first among CAR-T patent applicants, Immatics Biotechnologies GmbH does not appear prominently among the central nodes. This may indicate specialized patenting strategies or niches that differ significantly from broader network trends, warranting further exploration.

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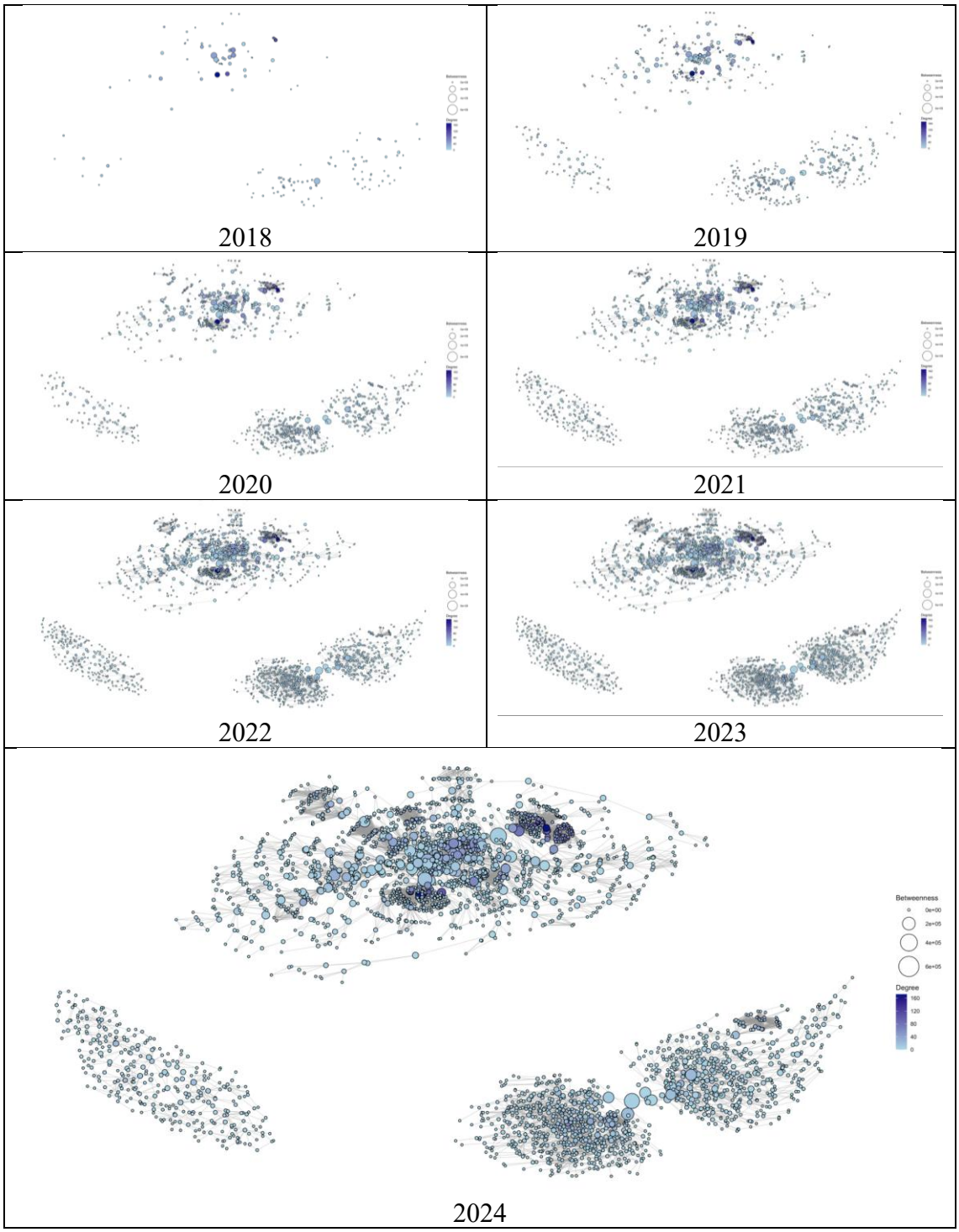
CRISPR

Table 4-10

The Patent Citation Network of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) by Year (2018-2024)



Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

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The citation network of CRISPR is composed of three clusters. The top cluster includes patents with the highest degree of centralization. It was still in pieces before 2021, when some patents were granted and linked together, forming the current appearance of the cluster. Meanwhile, the bottom right cluster initially consisted of two separate clusters, and it was not until 2022 that a key patent linked them together. Unlike the other two, the bottom-left cluster has remained isolated and dispersed throughout, showing no tendency to connect with the other clusters.

From the labels generated by GPT-4, two-thirds of the CRISPR clusters are agriculturally related, specifically to the development of soybean cultivars, maize hybrids, and inbred varieties. The third one (cluster e) is labeled “advanced genome engineering and therapeutic applications in CRISPR,” but no trajectory was found.

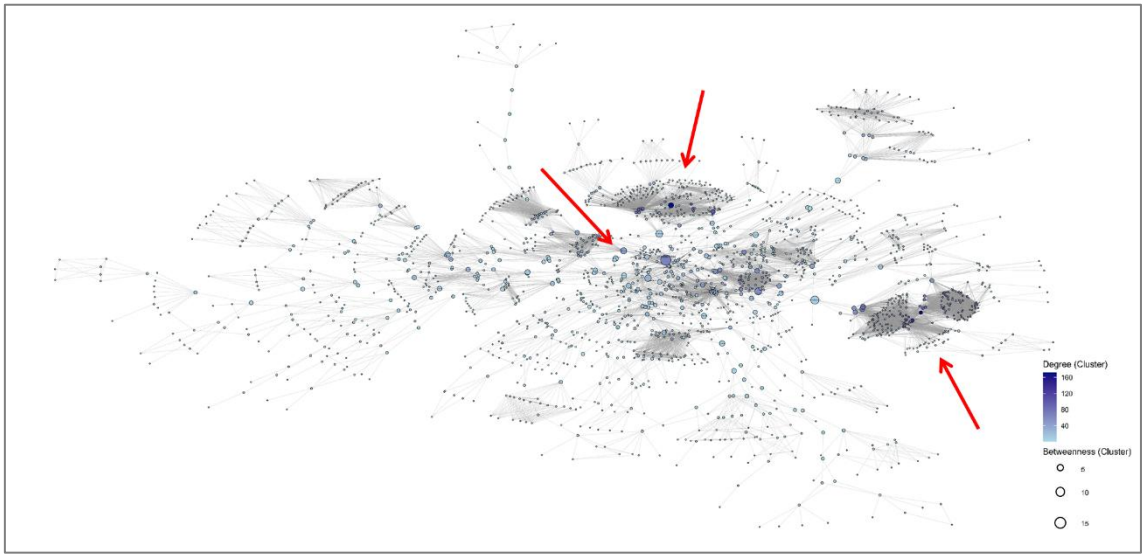

Figure 4-9

Cluster (e) of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Patent Citation Network (2011-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

There are three dense parts in cluster (e) (marked with arrows in **Figure 4-9**) that the

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researcher considered more noticeable throughout the entire web-like structure; each of them has one or two patents that hold important positions in the nearby network.

Two intensive citing relation patents in the bottom right part of the cluster are NO. US10273541B2 and NO. US10011872B1, both disclosing compositions, methods, systems, and devices for polynucleotide processing by 10X Genomics Inc. (Belgrader et al., 2018; Hindson et al., 2019). A high betweenness patent links between the bottom-right network and the middle one is NO. US11753677B2, a patent covering methods and kits for creating single-cell barcodes and attaching them to molecules within a single cell by Encodia Inc. (Chee et al., 2023).

The middle network exhibits a rather loose structure without a relatively centralized patent, but one high betweenness patent is observed, NO. US11866726B2. It introduces a genome editing system using donor templates with integrated priming sites, enabling precise targeted integration and quantitative detection of all on-target editing outcomes (Cotta-Ramusino & Margulies, 2024). It is further connected to the left network via NO. US10066233B2 as one of the routes. NO. US10066233B2 is a method of modulating cell resistance (Barrangou et al., 2018). The small network that it connects to on the left side includes methods and compositions for guiding Cas9 targeting sequences, developed at North Carolina State University (Barrangou & Briner, 2020), and a group of patents held by SNIPR Biome ApS, disclosing topics related to microbial infections and altering microbial for immune modulation (Clube, 2019, 2021, 2022; Clube et al., 2023; HAABER et al., 2024; Sommer et al., 2022a, 2022b).

The top part of the cluster includes the patent with a high degree in both centrality and betweenness, which is NO. US10017760B2. The patent introduces methods and compositions for trackable genetic variant libraries. Another patent, which also has high betweenness but less centrality, is located in the top part of the cluster, NO.

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US10011849B1. Inscripta Inc. holds and discloses nucleic acid-guided nucleases, guide nucleic acids, and targetable nuclease systems, which can be used for editing genetic targets, including recursive and trackable genetic engineering methods (Gill et al., 2018).

Inscripta also has a patent related to cell or genome editing in yeast (Kannan et al., 2021; Stefani & Gander, 2022), and the invention describes an automated multi-module system and method that enables recursive genome editing in live cells, with automated removal of editing vectors used in previous rounds (Tian et al., 2020).

To the left side of NO. US10017760B2, a minor group of patents, mainly constituted by patents from Zymergen Inc., surrounding HTP genomic engineering and improving host cells (Zach Serber et al., 2021; Zachariah Serber et al., 2021; Serber et al., 2022a, 2022b).

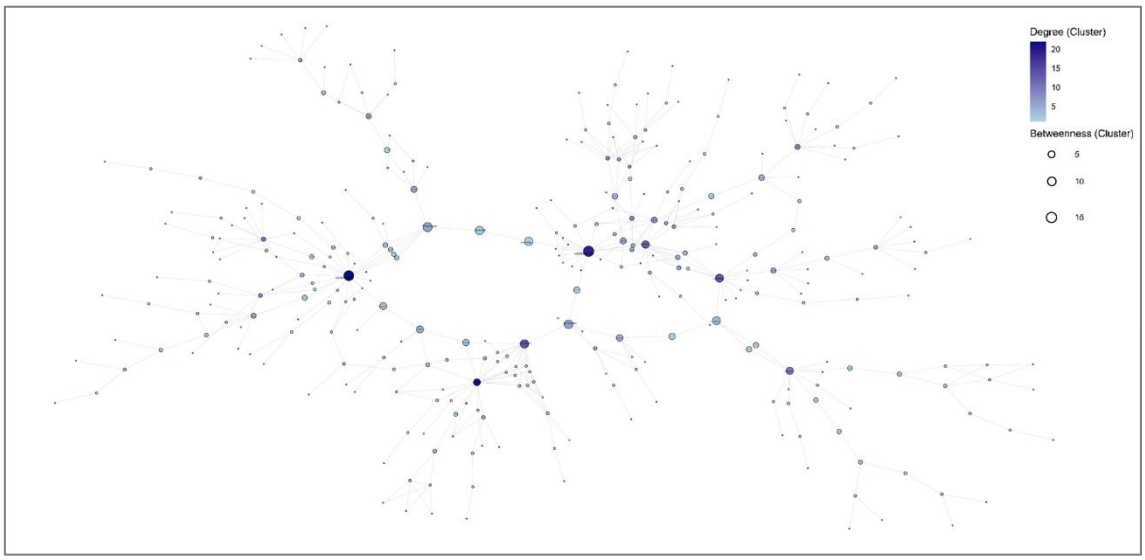

Figure 4-10

Cluster (f) of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Patent Citation Network (2011-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (f) is centered by a circle composed of twelve nodes, and nine of them have

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an extended network that forms four branches out of the center circle. The entire cluster has only one theme: soybean cultivars (Mason, 2019, 2021a, 2021b, 2022a, 2022b). All the patents were applied for by M.S. Technologies LLC, a company focused on traits, technology, and soybean genetic innovations to advance the future of farming (MS Technologies, n.d.).

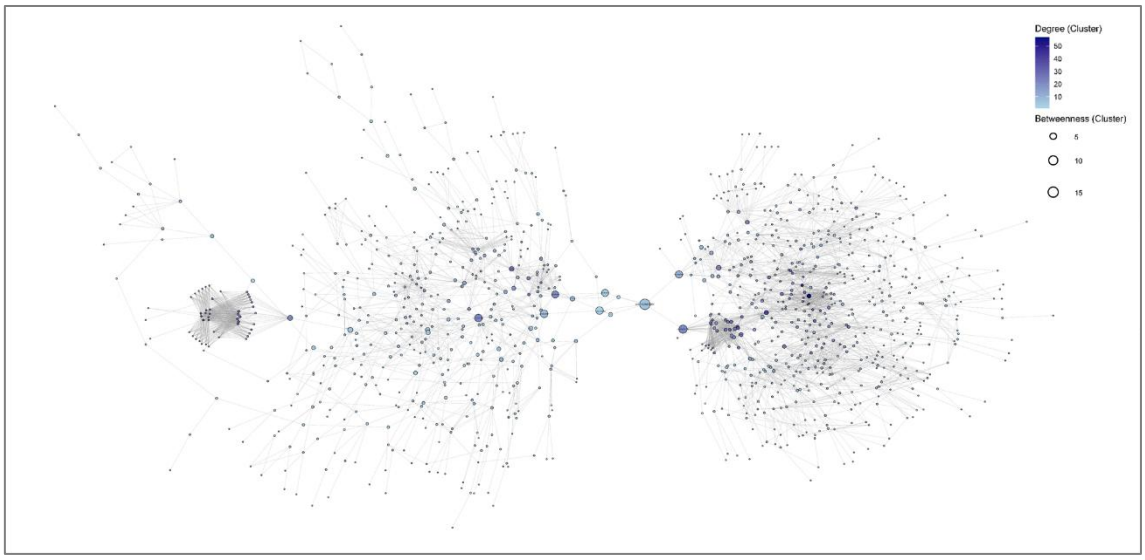

Figure 4-11

Cluster (g) of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Patent Citation Network (2011-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

The structure of the cluster (g) is a classic bowknot shape. The two sides have only one intersection point, NO. US11528874B1, which Pioneer Hi-Bred International Inc. holds, describes a new X15P092 hybrid maize variety (Crowley, Cunnyngham, Henry, et al., 2022). The company is ranked 1st among the primary applicants, holding 1,701 patents and accounting for 12.17% of the dataset.

The left part is a looser network than the right. The theme follows the intersection point: a large part of the patents are maize hybrid or inbred-related patents held by Pioneer

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Hi-Bred International (Barker et al., 2019; Crowley, Cunnyngham, Gadlage, et al., 2022; Fox et al., 2021; Holley, 2020). On the far-left side, a small and dense network has formed, starting from patent NO. US11716945B2. The patent and the following small network disclose inbred corn lines held by KWS SAAT SE and Limagrain Europe SA (Amusan, 2019; Popelka, 2023).

As for the right part of the bowknot structure, it is mainly composed of the hybrid corn varieties by Monsanto Technology LLC (Asoro et al., 2018; Bhatnagar et al., 2022; Bhatnagar et al., 2024; Buffard et al., 2019, 2023; Chopin et al., 2019; Lubich & Nichols, 2022).

Table 4-11

Summary for Clusters of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Patent Citation Network (2011-2024)

Cluster	No. of Patents	Technology Trajectory	GPT-4 Generated Label	Important Patents
(e)	1,952	No	Advanced Genome Engineering and Therapeutic Applications of CRISPR	US10017760B2* US11866726B2**
(f)	319	Yes	Elite Soybean Cultivar Development and Breeding	US10506785B1*** US10064361B1*** US11337397B2*
(g)	1,110	Yes	Maize Hybrid and Inbred Varieties for Seed Production	US11606924B2* US11528874B1**

Note. Data compiled by the researcher. * represents a high degree in centrality; ** represents a high degree in betweenness; *** represents a high degree in both.

From observing the three clusters of CRISPR, it is evident that the technology is primarily used in the fields of agriculture and medicine. While CRISPR's patent citations in agriculture tend to cite patents from the same company and, from there, form a large network, the citation pattern in medical and clinical applications remains diversified, with

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no indication of a dominant trajectory emerging yet.

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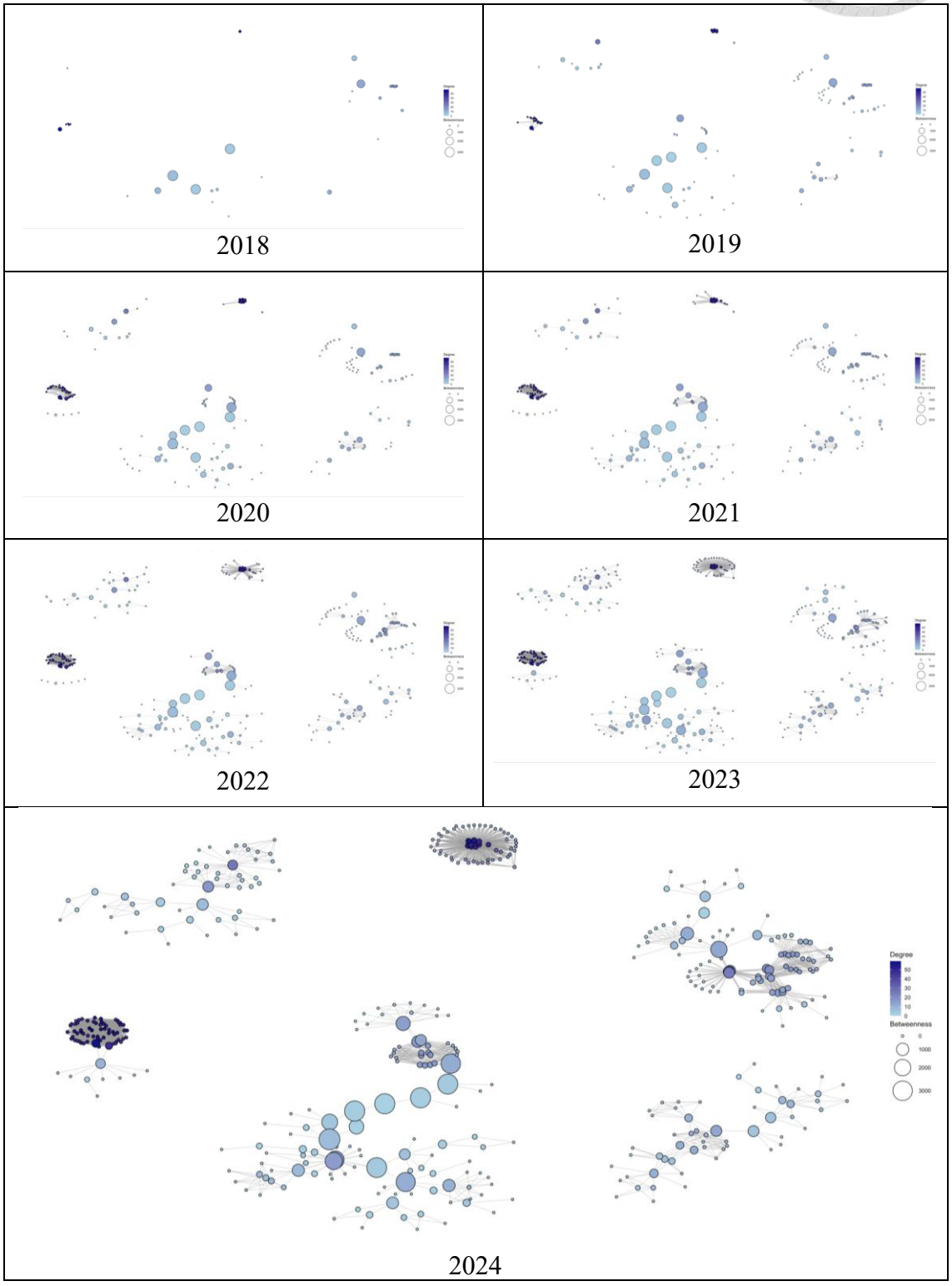
MSC

Table 4-12

The Patent Citation Network of Mesenchymal Stem Cell (MSC) by Year (2018-2024)



Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

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The network of MSC is fragmented. In the past few years, each cluster has developed separately into different patterns, and currently, there are no signs of merging or a trajectory forming across the clusters.

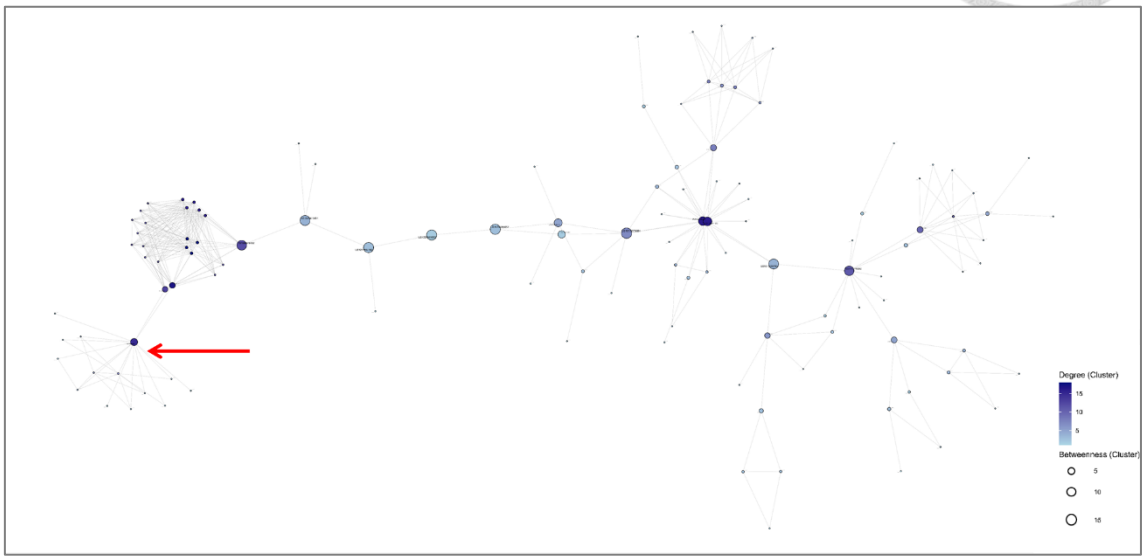

Figure 4-12

Cluster (h) of Mesenchymal Stem Cell (MSC) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

A main pathway constitutes the main structure of Cluster (h) and surrounds musculoskeletal topics.

From the left, patent NO. US10254274B2 (marked with an arrow in **Figure 4-12**) from Milica Radisic discloses methods, compositions, and devices for 3D biological tissues (Miklas et al., 2019). It then links to NO. US11951018B2 and NO. US10940015B2, the two patents from the Institute for Musculoskeletal Science and Education Ltd. (IMSE) that introduce implants with bone-contacting elements (Sack, 2021, 2024). The three patents jointly interweave a small web-like network on the left. The two IMSE patents are linked to NO. US10660764B2, which describes bone scaffolds for spinal fusion by the Stevens Institute of Technology (Maglaras & Valdevit, 2020).

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The pathway is then developed to the right by a series of patents from Warsaw Orthopedic Inc. and Musculoskeletal Transplant Foundation, describing patents such as bone graft, bone fibers, tissue engineering, and 3D biomedical material printing (McAllister et al., 2020; McAllister et al., 2023; Miklas et al., 2019; Rhodes & Shimko, 2024; Schlachter et al., 2019; Semler et al., 2018; Wei, 2018). Warsaw Orthopedic Inc. is ranked second among primary applicants of MSC and holds 187 patents (see **Table 4-4**); the Musculoskeletal Transplant Foundation is ranked 27th.

At the end of the pathway, NO. US11938245B2 and NO. US11806443B2, which both disclose cartilage-derived implants (Nasert et al., 2023, 2024), develops a radial shape centered by them. Above the radial star, a patent presenting adipose tissue-derived matrix is also provided by the Musculoskeletal Transplant Foundation (Huang et al., 2018).

As labeled by GPT-4, the cluster is themed by “tissue-derived biomaterials and regenerative implants”. It includes technologies spanning from decellularization, 3D printing, tissue processing, and scaffold fabrication to create biocompatible implants, grafts, and cell culture platforms for orthopedic, cardiovascular, urologic, and aesthetic applications.

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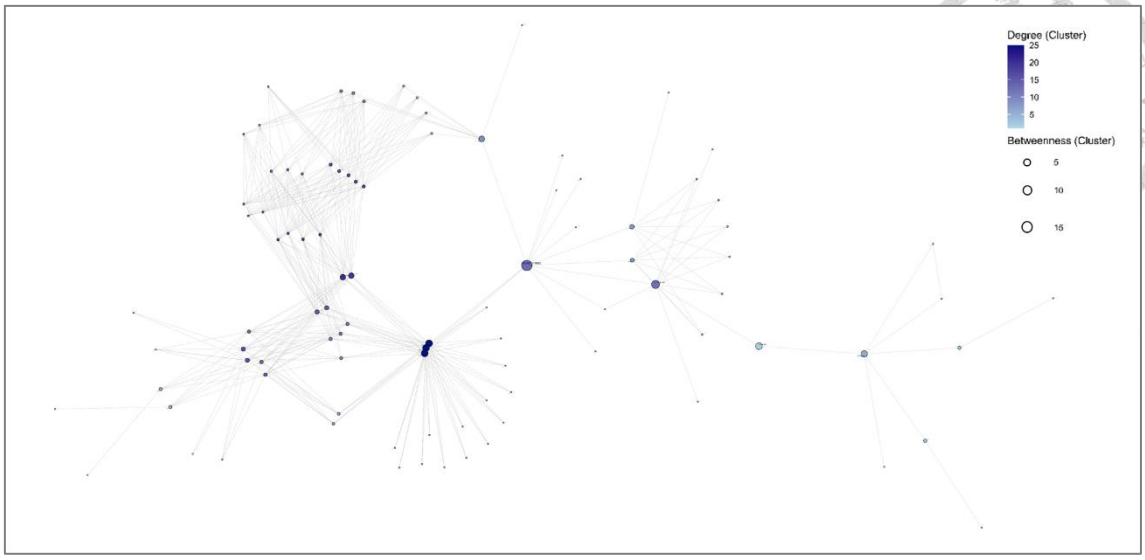

Figure 4-13

Cluster (i) of Mesenchymal Stem Cell (MSC) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (i) presents the technology network of the German company Immatics Biotechnologies GmbH, which was the 3rd in the primary applicants. Similar to the label of summary generated by GPT-4, the patents cover topic related to peptides or antibodies used in immunotherapies against various types of cancers, including hepatocellular carcinoma, small-cell lung cancer, ovarian cancer, and gastrointestinal and gastric cancers (Fritsche et al., 2021, 2022a, 2022b, 2023; Mahr et al., 2021; MAHR et al., 2024a, 2024b, 2024c; Weinschenk, Mahr, et al., 2018, 2023; Weinschenk, Walter, et al., 2018, 2023, 2024).

The cluster has strong mutual citing relations on the left part. It is highly centered on three consecutive patents related to peptides for immunotherapies (NO. US11912749B2, NO. US11912748B2, and NO. US12071458B2) and further extended by NO. US10071148B2, which presents immunotherapy for several lung-related cancers (Weinschenk, Walter, et al., 2018).

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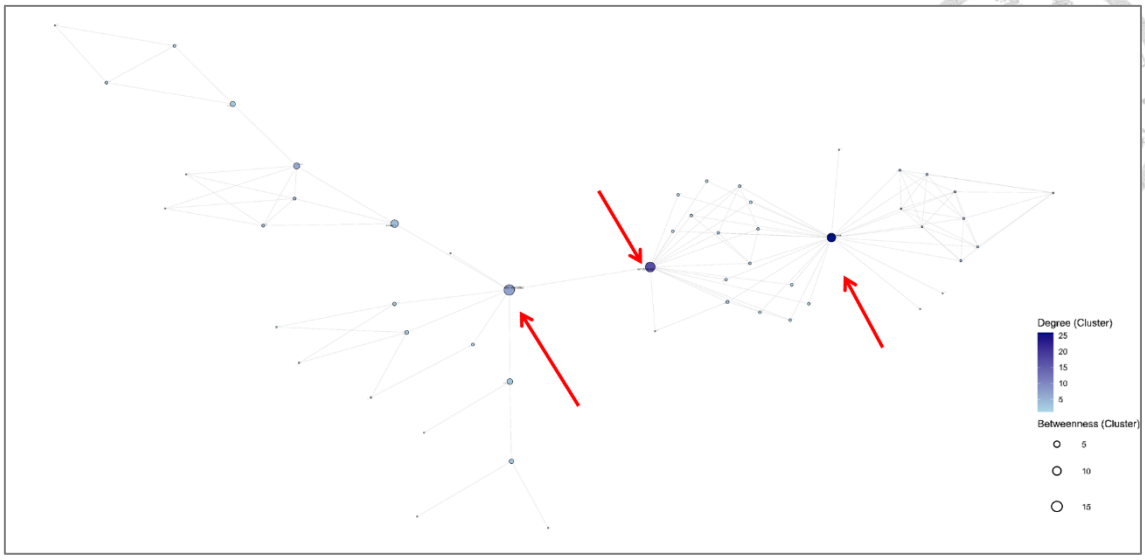

Figure 4-14

Cluster (j) of Mesenchymal Stem Cell (MSC) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (j) encompasses a substantial group of patents related to CRISPR technology, aligning with the results from GPT-4. The cluster is divided into three parts by three significant nodes that have either high centrality or betweenness (marked with arrows in **Figure 4-14**). Each part has a specific combination of the assignees.

From left to right, the three significant nodes have all been captured in the clusters of CRISPR, showing that important patents can create influence across different technology networks. They are:

- NO. US11866726B2 from Editas Medicine Inc., disclosing a system for the detection and measurement of possible gene editing outcomes (Cotta-Ramusino & Margulies, 2024).
- NO. US10570415B2 from the Regents of the University of California (UC), which provides RNA-guided nucleic acid modifying enzymes (DOUDNA, Banfield, et al., 2020).

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- NO. US10253365B1, also from UC, describes compositions and methods for detecting target DNA (DOUDNA et al., 2019).

On the right side of NO. US10253365B1, a small network can be found. It includes patents from different academic units, such as the NO. US11118224B2 from UC describing Type V CRISPR effector proteins (Doudna et al., 2021); NO. US12091709B2, NO. US10669540B2, and NO. US11091798B2 from the Massachusetts Institute of Technology, Broad Institute Inc., and Harvard University, providing CRISPR enzymes and systems (Zhang et al., 2021, 2024; Zhang et al., 2020).

Between NO. US10570415B2 and NO. US10253365B1 is another small network. UC and Scribe Therapeutics Inc. mainly hold the patents here. The patents of UC surround CRISPR effector polypeptides (Doudna, Al-Shayeb, et al., 2023a, 2023b; Doudna, Banfield, et al., 2023; DOUDNA et al., 2024), while Scribe's are focusing on engineered proteins in gene editing systems and guiding nucleic acid scaffolds (Oakes et al., 2023, 2024).

The last network is located on the left side of NO. US11866726B2. The mutual citations here are fewer than in the previous two networks, presenting an open system that expands more widely and includes additional assignees. NO. US10196651B2, applied by Sangamo Therapeutics, discloses a CRISPR nuclease that cleaves the BCL11A gene (Conway et al., 2019). Leland Stanford Junior University has several patents in the network too, describing different implementations of CRISPR on primary cells (Dever et al., 2021, 2022, 2023; Porteus et al., 2023). Other companies that can be found on this network include Editas Medicine Inc., Massachusetts Institute of Technology, Broad Institute Inc., and Agilent Technologies Inc. They work jointly to apply for patents found in the network (Porteus et al., 2022; Zhang et al., 2019).

Among the applicants captured in the cluster, Leland Stanford Junior University is

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the highest ranking, ranking number four among the primary applicants. It is followed by Harvard University, which ranks fifth; Massachusetts Institute of Technology, which ranks ninth; Sangamo, ranking thirty-seventh; and Broad Institute Inc., ranking forty-first.

As for Editas and UC, which play a critical role in the cluster, they rank 137th and beyond 1,000, respectively. This suggests that in the field of patent strategy, the number of patents held is not the most important factor, but instead, whether the patent is strategically positioned to create the greatest impact on the technology network.

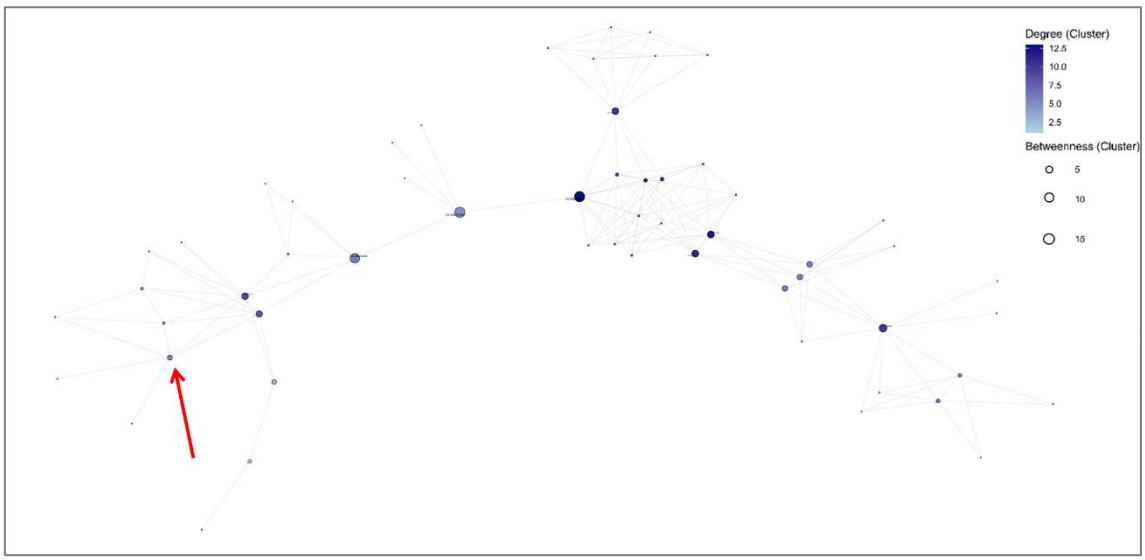

Figure 4-15

Cluster (k) of Mesenchymal Stem Cell (MSC) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

A clear pathway can be found in the cluster (k). There are eight nodes on the path, covering topics related to cell therapies, regenerative platforms, and their applications.

The first few nodes from the left (marked with an arrow in **Figure 4-15**) are patents from Astellas Institute for Regenerative Medicine (AIRM), NO. US10485829B2. It presents an invention that improved the production of retinal pigmented epithelial (RPE) cells from various types of stem cells (Malcuit et al., 2019). NO. US11680941B2 and NO.

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US11422125B2 discloses a new assay to test the function of PRE cells (Klimanskaya et al., 2023; Klimanskaya et al., 2022). NO. US10894065B2 provides a production process for pluripotent stem cells (Feng et al., 2021).

NO. US12060576B2 from Stellular Bio discloses methods for megakaryocyte production (Thon & Dykstra, 2024). NO. US10869898B2 is the patent with the most centrality degree in the cluster, related to cells containing exogenous antigens (Mata-Fink et al., 2020). Along with the following two patents, NO. US10456421B2 and NO. US10329531B2, the three patents form a little network, while Rubius Therapeutics is the mutual assignee.

The subsequent three patents on the path are NO. US11674121B2, NO. US12049644B2, and NO. US11248213B2, all of which originate from the University of California and describe compositions of cytoplasts and methods for their use in treatment (Klemke & Wang, 2022, 2023, 2024). Lastly, the technology path develops to NO. US10105436B2, a patent from Calidi Biotherapeutics disclosing a smallpox vaccine for cancer treatment (Szalay & Minev, 2018).

As concluded by GPT-4, the cluster is labeled “cell engineering platforms for regenerative and immuno-oncology therapies”.

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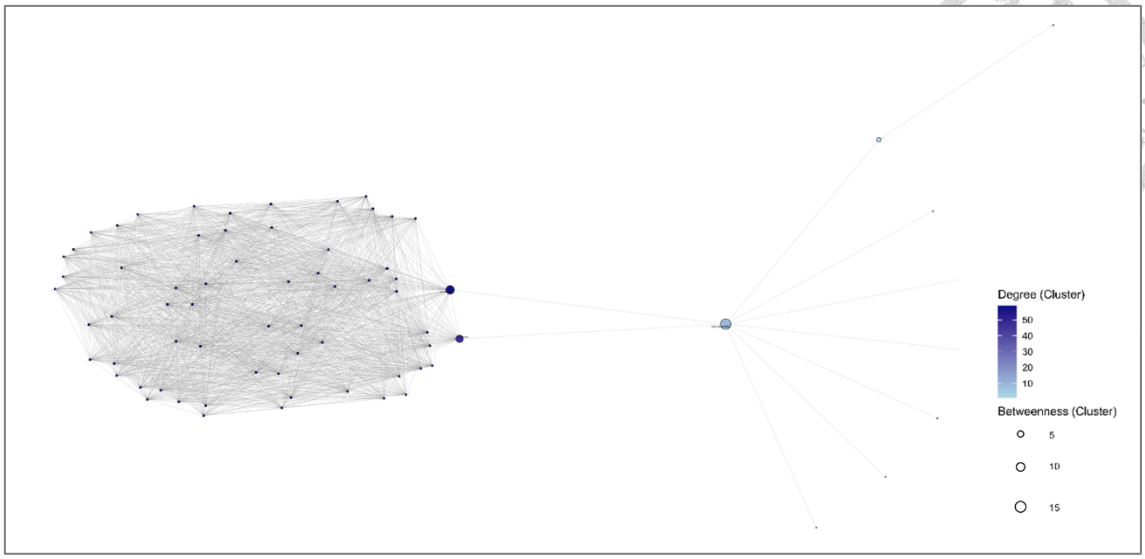

Figure 4-16

Cluster (l) of Mesenchymal Stem Cell (MSC) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

The cluster (l) is composed of two parts. The left part, featuring a dense network, is centered and interweaved by two patents: NO. US10092288B2 and NO. US10729430B2. The two patents are both held by Biomet Sports Medicine, which ranks 12th among the primary applicants. They provide a method and apparatus for coupling a soft tissue implant into a bone with a locking cavity (Denham & Stone, 2018, 2020).

As for the right part of the cluster, NO. US11826489B2 links the above two patents and starts another loose network with eight patents included so far. The patent discloses methods of preparing and using collagen scaffolds (Murray, 2023). It is applied and assigned by the Children's Medical Center Corporation, ranking 35th among the primary applicants.

However, Children's Medical Center Corporation is not the only medical institution captured in the right network. Boston Children's Hospital and the Cleveland Clinic Foundation are among them as well, suggesting a shift in the patent field, moving from

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technology providers like Biomet Sports Medicine to medical service providers.

The cluster is labeled “soft tissue fixation and ligament repair technologies” by GPT-4.

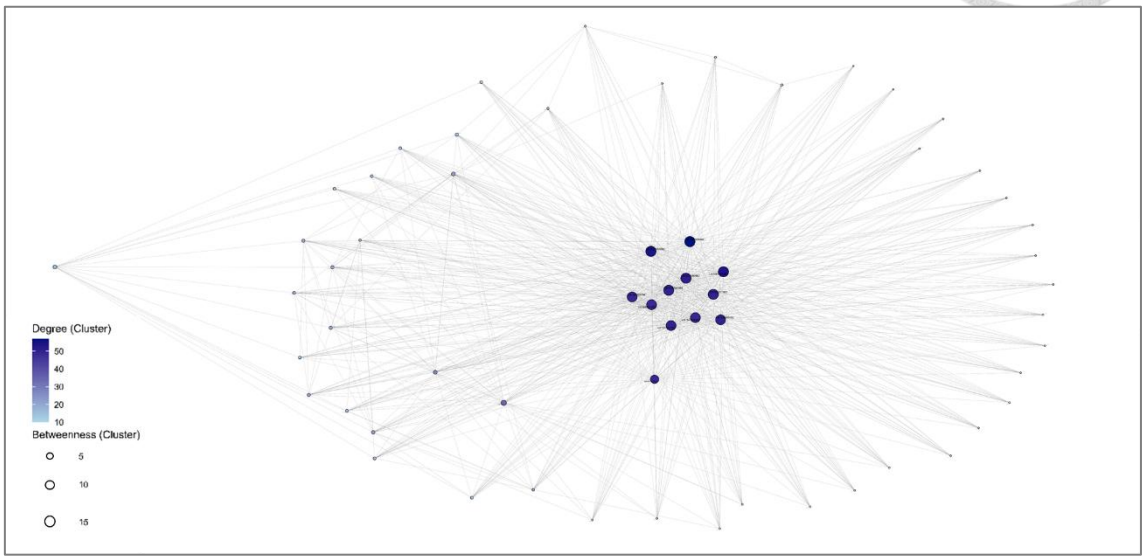

Figure 4-17

Cluster (m) of Mesenchymal Stem Cell (MSC) Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (m) is a giant interweaving radial star centered by 13 patents, all held by DePuy Synthes Products, Inc., the company ranking 6th among all primary applicants. NO. US10238500B2 is an invention related to an intervertebral motion disc (Rogers et al., 2019). NO. US10085843B2, NO. US10555817B2, NO. US10492918B2, NO. US10433971B2, NO. US10575959B2, NO. US10639164B2, NO. US10583013B2, NO. US10376372B2, NO. US10405986B2, and NO. US10420651B2 all describe an orthopedic device for implanting (DiMauro, 2018, 2019; DiMauro & Malone, 2019; Thomas M. DiMauro & Michael Andrew Slivka, 2020a; Thomas M. DiMauro & Michael Andrew Slivka, 2020; Thomas M. DiMauro & Michael Andrew Slivka, 2020; Thomas M. DiMauro & Michael Andrew Slivka, 2020b; Kelly & DiMauro, 2019;

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Serhan et al., 2019a, 2019b). NO. US10973652B2 is positioned slightly farther from the other 12 patents, providing a design of a fusion cage (Hawkins et al., 2021).

As labeled by GPT-4, the theme of the cluster is “expandable and in-situ intervertebral fusion devices,” used to improve spinal stability, fusion outcomes, and surgical ease.

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Table 4-13

Summary for Clusters of Mesenchymal Stem Cell Patent (MSC) Citation Network (1976-2024)

Cluster	No. of Patents	Technology Trajectory	GPT-4 Generated Label	Important Patents
(h)	120	Yes	Tissue-Derived Biomaterials and Regenerative Implants	US11938245B2* US11806443B2* US10254274B2*
(i)	95	No	Peptide-Based Personalized Cancer Immunotherapies	US11912749B2* US11912748B2* US12071458B2* US10071148B2**
(j)	53	No	CRISPR Systems and Precision Genome Editing Technologies	US10253365B1* US10570415B2*** US11866726B2**
(k)	56	Yes	Cell Engineering Platforms for Regenerative and Immuno-Oncology Therapies	S10869898B2***
(l)	72	No	Soft Tissue Fixation and Ligament Repair Technologies	US10092288B2* US11826489B2**
(m)	60	No	Expandable and In-Situ Intervertebral Fusion Devices	US10238500B2*** US10085843B2*** US10575959B2*** US10639164B2*** US10433971B2*** US10583013B2*** US10555817B2*** US10492918B2*** US10376372B2*** US10405986B2*** US10420651B2***

Note. Data compiled by the researcher. * represents a high degree in centrality; ** represents a high degree in betweenness; *** represents a high degree in both.

Overall, the MSC patent landscape remains dispersed across orthopedic, immunotherapy, CRISPR-related, and regenerative domains. Each cluster represents a distinct technical focus with limited cross-cluster integration, indicating a diversified but uncoordinated state of development without a dominant technological trajectory.

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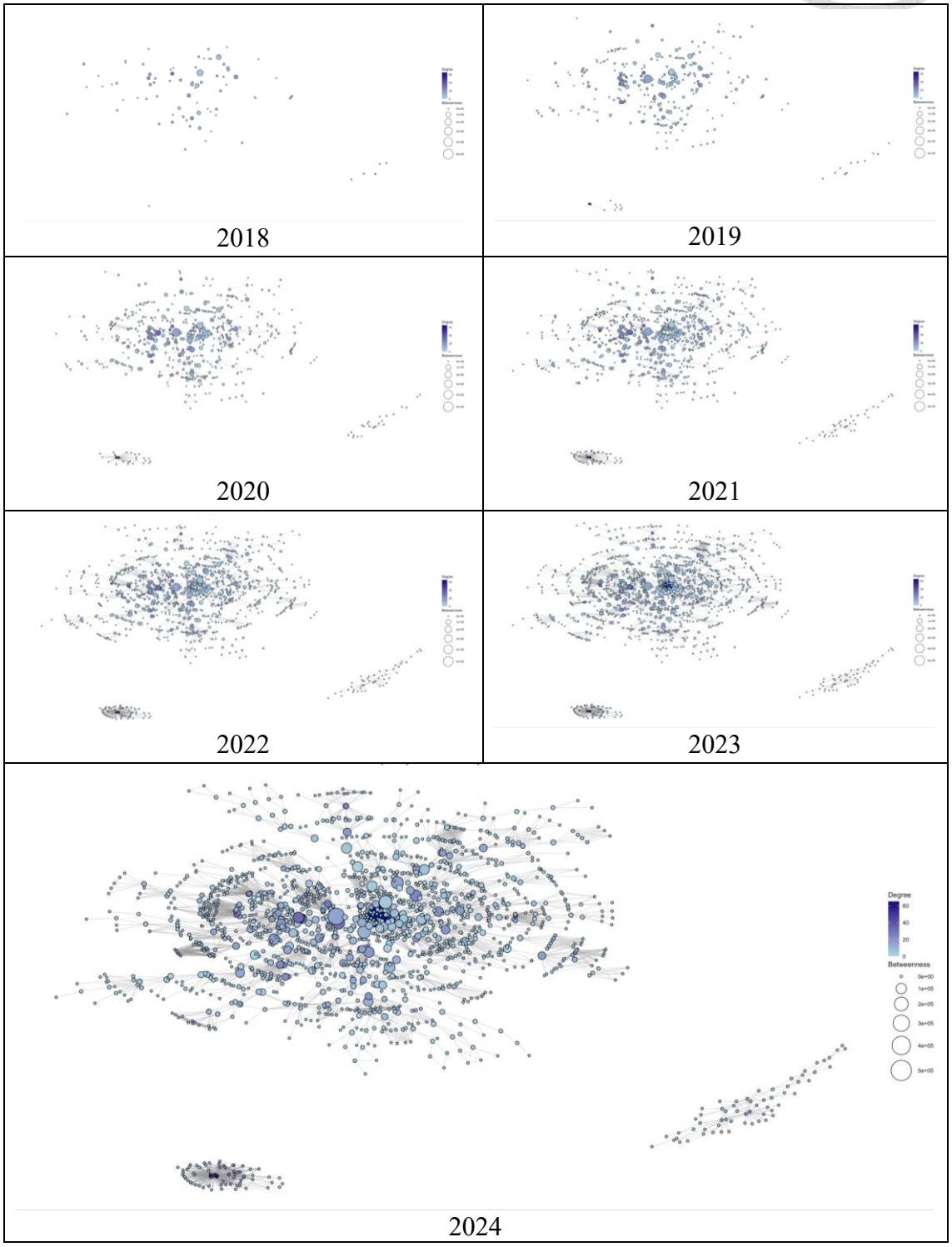
NK Cell

Table 4-14

The Patent Citation Network of Natural Killer Cells by Year (2018-2024)



Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

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The development of technology in NK cells resulted in three distinct clusters. Cluster (n), at the top, was the first to establish its network, whereas clusters (o) and (p) began to emerge after 2020.

At present, the patterns of the three clusters differ, and no indications of merging have been noted. This may suggest that the primary technological trajectory for NK cell implementation is still in development.

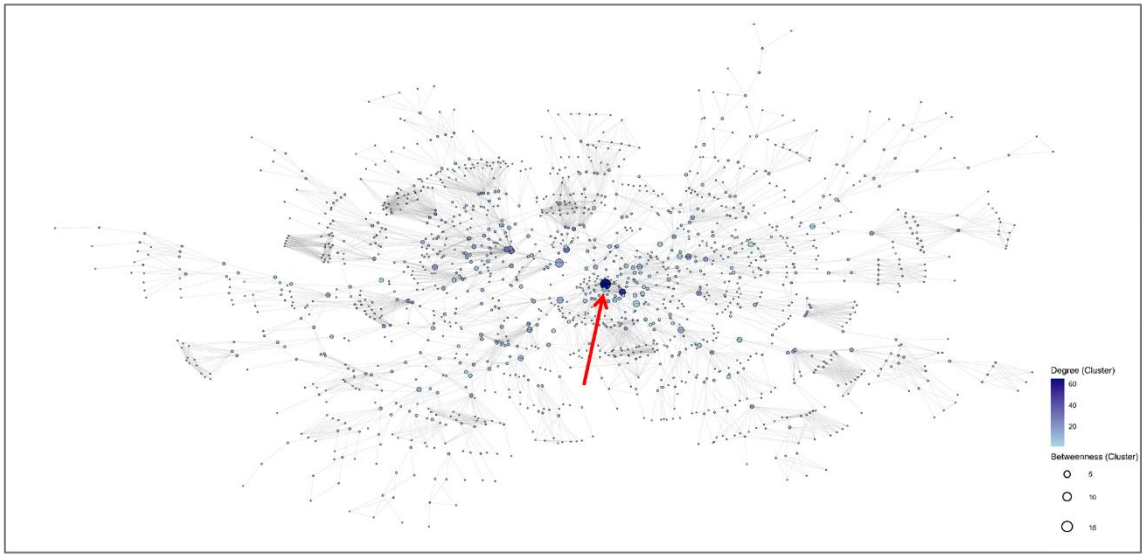

Figure 4-18

Cluster (n) of Natural Killer Cell Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (n) is a giant web-like structure. As summarized by GPT-4, the patents captured in this cluster focus on next-generation immunotherapies, particularly CAR technologies, engineered immune cells, and methods for enhancing immune tolerance and cell-based cancer treatments. The concentration is evident in some key nodes within the clusters.

For example, the patent with the highest centrality degree and betweenness is patent NO. US11661459B2 (marked with an arrow in **Figure 4-18**). This patent covers

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polynucleotides that encode inactivated cell surface receptors, which are genetically engineered iPSCs, and derivative cells expressing CAR (Naso et al., 2023). Next to it, NO. US11883432B2 is found; the betweenness is smaller, but the centrality degree is similar. The patent discloses CARs that have adaptable receptor specificity (Carton et al., 2024). Both patents have been mentioned in the previous treatment.

NO. US10358477B2 is a patent with a degree of less centrality but holds the second-highest betweenness in the cluster. The patent presents an invention related to simulating the IL-15Rbeta/gamma signaling pathway, thereby triggering the activation of cells such as NK or T cells (Jacques et al., 2019). The patent is held by the Institut National de la Santé et de la Recherche Médicale (INSERM), a French public scientific and technological institute founded in 1964, operating under the joint authority of the French Ministries of Health and Research. (Inserm, n.d.). INSERM is ranked 38th among the primary applicants of NK cells.

Another patent with a lower betweenness but higher degree of centrality than NO. US10358477B2 is NO. US12104178B2. This patent describes an invention that relates to the composition and methods for regulating and controlling the expression of proteins (Suri et al., 2024).

Notably, five patents are closely positioned together, held by Pandion Therapeutics and Pandion Operations. These patents describe methods and compounds that confer site-specific or local immune privilege (Higginson-Scott et al., 2023; Rios et al., 2024; Viney & Higginson-Scott, 2020, 2022; Viney et al., 2021).

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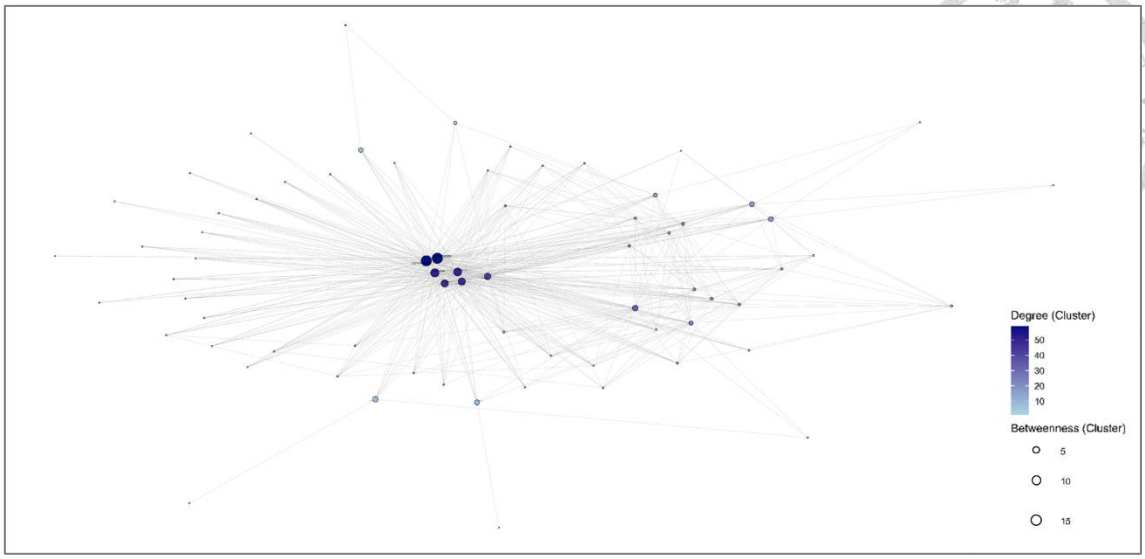

Figure 4-19

Cluster (o) of Natural Killer Cell Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (o) is an interwoven network formed by the patents from Amarin Pharmaceuticals Ireland. Amarin is the 17th primary applicant for patents related to NK cells. Headquartered in Ireland, this global pharmaceutical company is committed to enhancing cardiovascular health (Amarin, n.d.).

There are seven nodes, particularly centralized at the center of the clusters, which also exhibit the highest betweenness in the entire network. The most centralized and the second-most centralized patents are methods for reducing apolipoprotein C-III (Manku et al., 2019a, 2019b). The patents in the next tier, NO. US10278935B2 and NO. US10220013B2, respectively, disclose methods to lower the risk of cardiovascular events in patients undergoing statin therapy and approaches for managing mixed dyslipidemia (Osterloh et al., 2019; Soni, 2019).

The last three patents have equal centrality degree to the second tier but slightly less betweenness than the second tier. The patents also offer methods for lowering the risk of

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a cardiovascular event in individuals undergoing statin therapy (Soni, 2020a, 2020b, 2020c).

The theme label provided by GPT-4 highlighted omega-3, which appears twice in the patent titles of the cluster, as a specifically mentioned component in the patents.

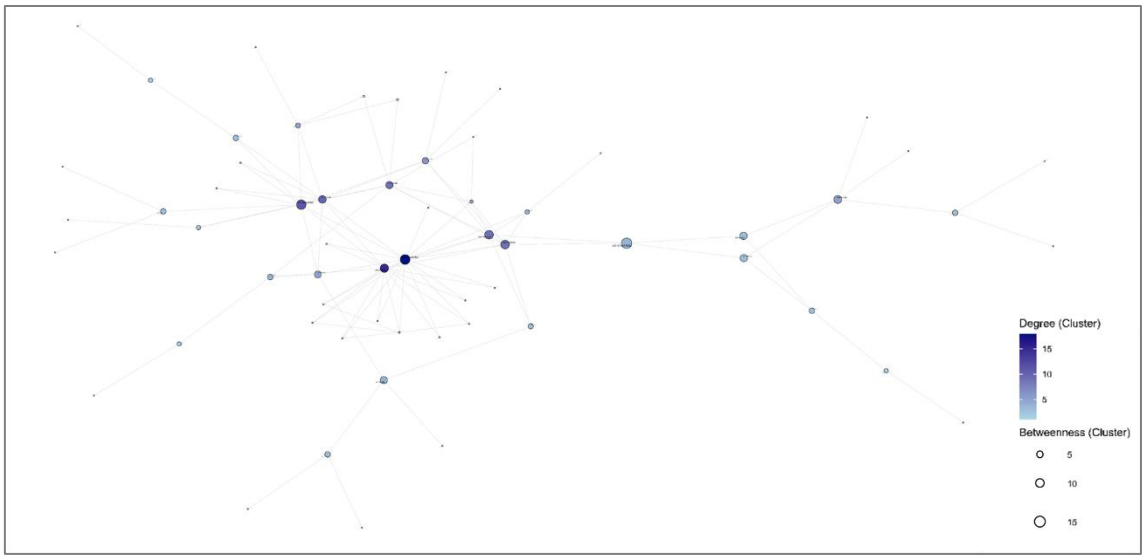

Figure 4-20

Cluster (p) of Natural Killer Cell Patent Citation Network (1976-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Cluster (p) resembles a neuron. A few more centralized patents comprise the "cell body" part, all of which relate to the T-cell immunoreceptor with Ig and ITIM domains (TIGIT), including agents that specifically bind to TIGIT and anti-TIGIT antibodies (Chand et al., 2022; Chand et al., 2021; Dupont & Parmar, 2021, 2022; Gurney & Xie, 2018; Maurer et al., 2019). The applicants for the patents include OncoMed Pharmaceuticals, Bristol-Myers Squibb Company, Agenus, and Mereo Biopharma 5. Bristol-Myers Squibb ranks 6th among the primary applicants.

As for the "axon" part, NO. US10144778B2 provides a pharmaceutical composition

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that contains an active agent capable of reducing the level of systemic immunosuppression (Eisenbach-Schwartz et al., 2018). NO. US11242385B2 and NO. US11098117B2 is also held by Agenus, disclosing antibodies that specifically bind to CD137 and enhance its function (Wilson et al., 2021; Xiao et al., 2022). This cluster highlights checkpoint-based approaches that interface with NK cell activation and inhibition, as labeled by GPT-4, “TIGIT and CD137 immune checkpoint antagonists for cancer immunotherapy”.

Table 4-15

Summary for Clusters of Natural Killer Cell Patent Citation Network (1976-2024)

Cluster	No. of Patents	Technology Trajectory	GPT-4 Generated Label	Important Patents
(n)	1,564	No	CAR and Immune Cell Therapies for Cancer	US11661459B2*** US11883432B2*
(o)	70	No	Omega-3 Therapies for Cardiovascular and Lipid Disorders	US10166209B2*** US10265290B2***
(p)	61	Yes	TIGIT and CD137 Immune Checkpoint Antagonists for Cancer Immunotherapy	US10112997B2*** US10144778B2**

Note. Data compiled by the researcher. * represents a high degree in centrality; ** represents a high degree in betweenness; *** represents a high degree in both.

Unlike the diversity of technology included in cluster (n), the formation of cluster (o) and cluster (p) is highly based on a company's focus or a target that inventors found potential in. Judging from their focus, the merging of cluster (n) and cluster (p) is more likely to occur, as they are both relevant to immunotherapies. However, the topic scope of the cluster (p) is still narrow; it may take some time for the cluster (p) to be included in cluster (n). By that time, perhaps a technological trajectory will be observed, too.

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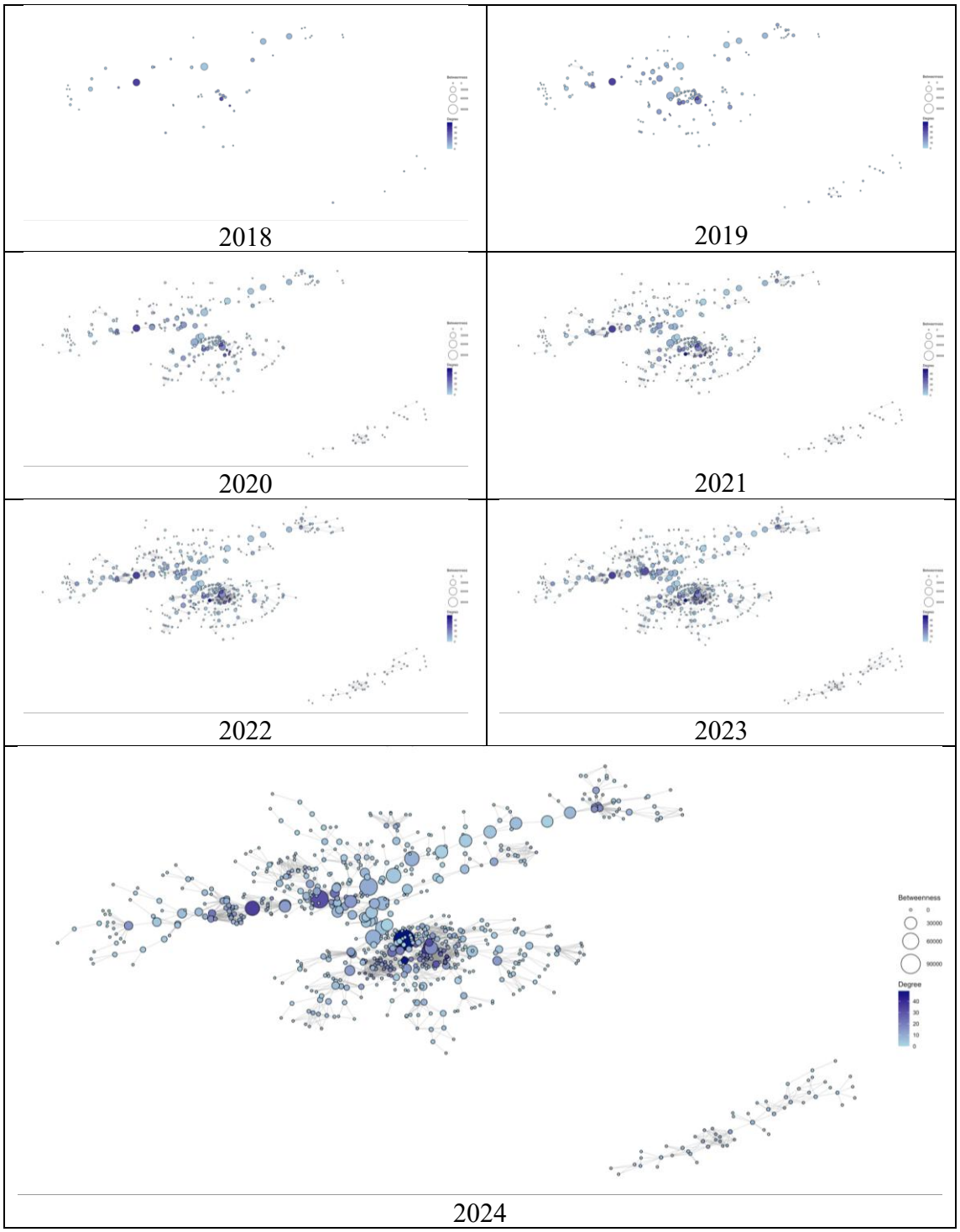
iPSC

Table 4-16

The Patent Citation Network of Induced Pluripotent Stem Cell (iPSC) by Year (2018-2024)



Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

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Table 4-16 shows the changes in iPSC's patent citation network by year. From 2018 to 2024, the number of patents related to iPSC has increased steadily, accompanied by an increase in the links between nodes. This suggests that citing relations and relevance are growing, with some major technologies being heavily cited and integrated, particularly after 2020.

Furthermore, the structure of the two clusters identified in the patent citation network of iPSC resembles a linear pattern more than a web-like configuration, suggesting that the formation of a technology trajectory may be in progress.

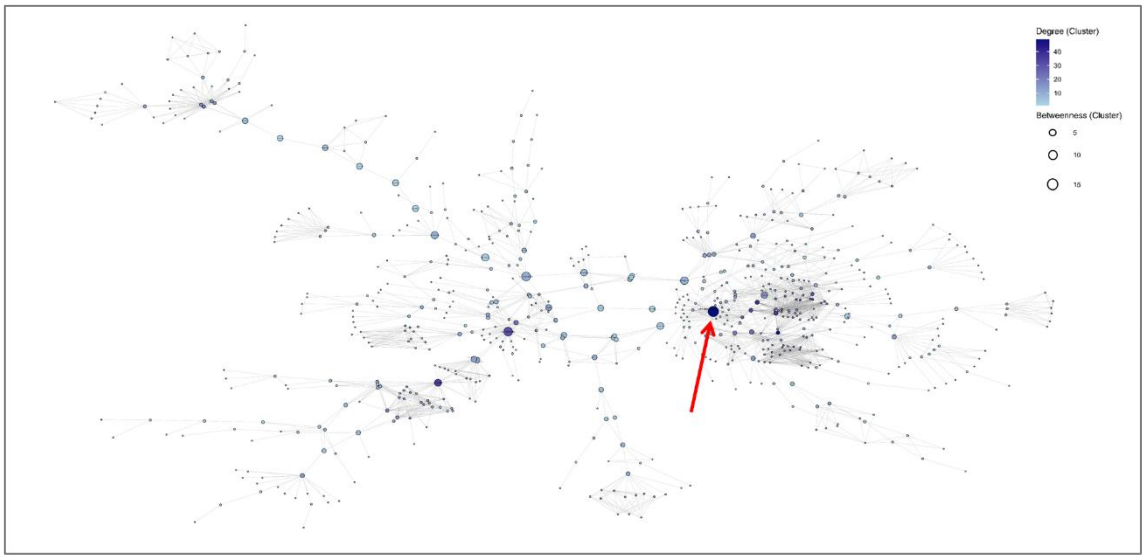

Figure 4-21

Cluster (q) of Induced Pluripotent Stem Cell (iPSC) Patent Citation Network (1982-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Two pathways are developing in cluster (q). The two pathways are eventually linked to a single node, which holds the highest centrality and betweenness in the cluster, NO. US11866726B2 (marked with an arrow in **Figure 4-21**). The patent from Editas Medicine describes a genome editing system capable of detecting and quantitatively measuring on-target gene modification outcomes (Cotta-Ramusino & Margulies, 2024). The patent is

doi:10.6342/NTU202502665

also included in the clusters of CRISPR and MSC. Editas ranks 31st among the primary applicants of iPSC.

The upper pathway begins at the top left corner from patents held by Children's Hospital Medical Center, which disclose methods for generating gastrointestinal organoids or tissue structures from precursor or pluripotent stem cells through directed *in vitro* or *in vivo* differentiation (J. Wells & K. McCracken, 2021; J. M. Wells & K. W. McCracken, 2021; Wells & Munera, 2023; Wells et al., 2023). The following patents on the pathway have similar betweenness and centrality, each from different companies in the industry.

- The University of California presents patents regarding the *in vitro* production of medial ganglionic eminence precursor cells and a conditionally active CAR and genetically modified cells to produce CAR (Nicholas et al., 2018; Wu et al., 2018).
- Whitehead Institute for Biomedical Research provides methods for reprogramming somatic cells (Jaenisch et al., 2018; Jaenisch & Hochedlinger, 2019).
- The Mclean Hospital Corporation discloses enhanced methods for generating medical ganglionic eminence (MGE) cells from pluripotent stem cells (Chung, 2023).
- Lyell Immunopharma, Inc. discloses methods of rejuvenated T cells production and encoded polynucleotides and CARs comprising a ROR1-binding protein and overexpressing a c-Jun polypeptide (S. PARK et al., 2024; Sakoda et al., 2024).
- Juno Therapeutics Inc. presents engineered cells for adoptive therapy that include NK cells and T cells (Mohler et al., 2020).

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- Arsenal Biosciences Inc. provides Immune cells that co-express shRNAs and logic gate systems (Williams et al., 2024).
- The University of Pennsylvania presents an invention related to compositions and methods for modifying T cells (Zhao et al., 2021).
- Harvard College discloses multiple patents related to universal donor stem cells and associated methods (Meissner et al., 2024a; Meissner et al., 2024b, 2024c). Also, jointly with The Children's Medical Center Corporation, they disclosed the patent on the therapeutic uses of genome editing with CRISPR/Cas systems (Musunuru et al., 2019).

The lower pathway begins at the lower left corner. Two patents have relatively high centralities in the path:

- NO. US10030229B2, held by Harvard College, discloses methods, compositions, kits, and agents used for triggering β cell maturation, as well as isolated populations of SC-β cells (Peterson et al., 2018).
- NO. US11661459B2 from Century Therapeutics provides polynucleotides encoded with inactivated cell surface receptors and genetically engineered iPSCs expressing CAR (Naso et al., 2023). It is also found in the network of AAV and NK cells.

Other patents that comprise the pathway are:

- NO. US10724052B2 and NO. US10865424B2, owned by Crispr Therapeutics AG, offers methods for generating genetically modified cells that are compatible with various subjects (Rezania & Ramos-Zayas, 2020a, 2020b).
- NO. US10287606B2 and NO. US10858628B2, both, applied by Fate Therapeutics, describe methods and compositions for obtaining genome-

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engineered iPSCs, as well as culture platforms, cell media, and techniques for differentiating pluripotent cells into hematopoietic cells (Valamehr et al., 2019; Valamehr et al., 2020).

- NO. US11377637B2, held by Memorial Sloan Kettering Cancer Center, provides a T cell integrated with one or more therapeutic transgenes, whose expression is controlled by an endogenous promoter (Sadelain et al., 2022).
- The assignee of NO. US10450585B2, owned by Sangamo Therapeutics, discloses genome engineering of a cell (Lee et al., 2019).
- NO. US10975149B2 from the Walter and Eliza Hall Institute of Medical Research describes therapeutic and prophylactic methods based on inhibition of CIS in NK cells (Huntington et al., 2021).
- NO. US11642374B2, NO. US11925664B2, and NO. US11903966B2 disclose methods of making and using genetically modified compositions, such as non-viral vectors and T cells, for cancer treatment. The three patents are the joint effort of the University of Minnesota, Intima Bioscience, Inc., and the US HHS (Moriarity et al., 2023; Moriarity, Webber, Choudhry, et al., 2024; Moriarity, Webber, Largaespada, et al., 2024).
- Finally, NO. US10570418B2 by the University of California discloses methods of site-specific modification of a target DAN and binding a target DNA in a eukaryotic cell (Doudna, Lin, et al., 2020).

GPT-4 summarizes the cluster as a cluster “centers on advanced biotechnological systems for precise genome editing, immune cell reprogramming, and stem cell differentiation.”.

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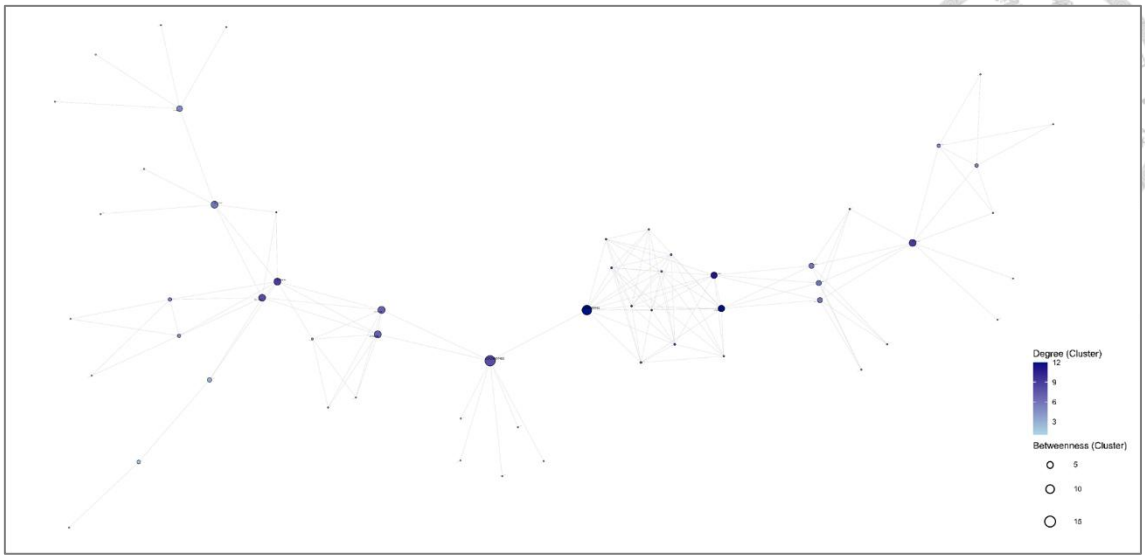

Figure 4-22

Cluster (r) of Induced Pluripotent Stem Cell (iPSC) Patent Citation Network (1982-2024)

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

The structure of cluster (r) follows a linear pattern. From left to right, the focus of the patent compositions transitions in order, covering the following topics:

- Ocular-related patents involve producing retinal tissues and photoreceptors from pluripotent stem cells, as well as developing new phagocytosis assays for testing the function of retinal pigment epithelium (RPE) cells (Klimanskaya et al., 2023; Klimanskaya et al., 2022; Lanza et al., 2019; Nukaya et al., 2024).
- Using iPSCs to produce platelets and megakaryocytes (Feng et al., 2019, 2021; Thon & Dykstra, 2024).
- Three patents that have the highest centrality in the cluster from Rubius Therapeutics focus on the functional modification and therapeutic application of blood or immune cells (Kahvejian, Mata-Fink, Deans, et al., 2019; Kahvejian, Mata-Fink, Round, et al., 2019; Mata-Fink et al., 2020).

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- The University of California provides a platform for generating safe cell therapeutics (Klemke & Wang, 2022, 2023, 2024).
- The last patent on the route, which is also the second-most central patent, is related to the smallpox vaccine used in treating cancer (Szalay & Minev, 2018). The patent was captured in the cluster of MSCs as well.

As labeled by GPT-4, cluster (r) is themed as "pluripotent stem cell-derived therapeutics and engineered cell platforms".

Table 4-17

Summary for Clusters of Induced Pluripotent Stem Cell (iPSC) Patent Citation Network (1982-2024)

Cluster	No. of Patents	Technology Trajectory	GPT-4 Generated Label	Important Patents
(q)	691	Yes	Gene and Cell Therapy Platforms for Regenerative Medicine and Immunotherapy	US11866726B2***
(r)	56	Yes	Pluripotent Stem Cell-Derived Therapeutics and Engineered Cell Platforms	US10869898B2*** US12060576B2**

Note. Data compiled by the researcher. * represents a high degree in centrality; ** represents a high degree in betweenness; *** represents a high degree in both.

The patents included in cluster (q) encompass several topics related to CGTs, such as CRISPR-Cas systems, RNA-guided genome editing, functionally improved CARs, universal donor cell platforms, and pluripotent stem cell-derived beta cell technologies. These innovations collectively highlight a broader strategic effort to address translational barriers in personalized immunotherapy, regenerative medicine, and *in vivo* gene correction.

Regarding cluster (r), the topics it covers are more diverse, illustrating a comprehensive strategy that integrates stem cell engineering, immunotherapy, and

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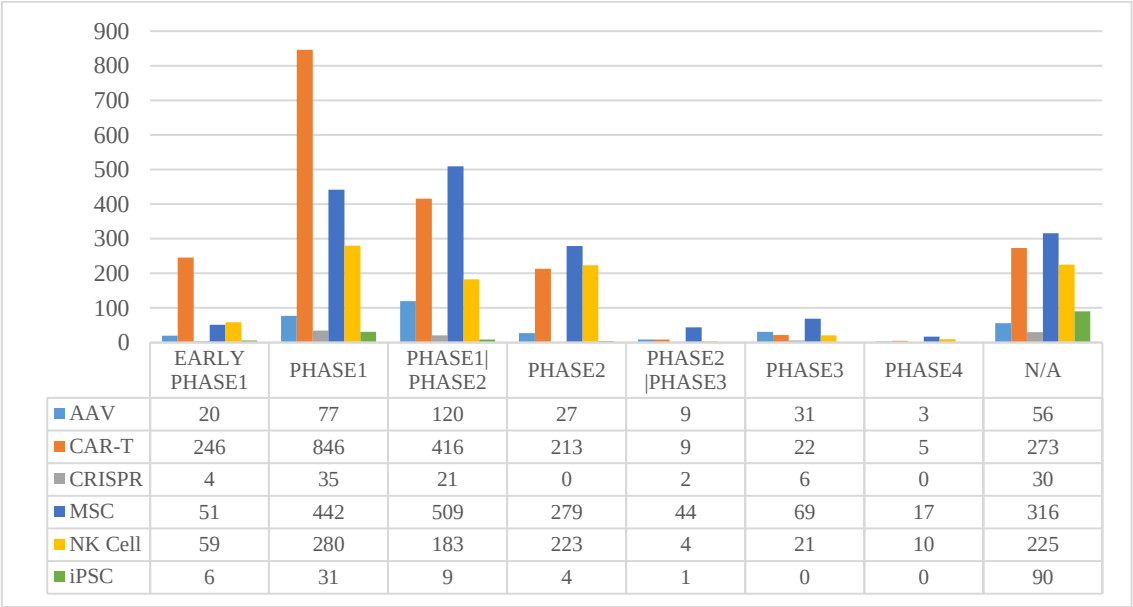
synthetic biology to tackle key challenges in the clinical translation of CGTs.

4.1.3 Therapy Indications and Technologies

There were 343 results for AAV, 2,030 results for CAR-T, 98 results for CRISPR, 1,728 results for MSC, 1,005 results for NK cells, and 140 results for iPSC.

As shown in **Figure 4-23**, only a small number of therapies have progressed to Phase III clinical trials. CAR-T and NK cells have the most trials in phase I, and MSCs have more trials in Phase I+II.



	EARLY PHASE1	PHASE1	PHASE1| PHASE2	PHASE2	PHASE2 |PHASE3	PHASE3	PHASE4	N/A
AAV	20	77	120	27	9	31	3	56
CAR-T	246	846	416	213	9	22	5	273
CRISPR	4	35	21	0	2	6	0	30
MSC	51	442	509	279	44	69	17	316
NK Cell	59	280	183	223	4	21	10	225
iPSC	6	31	9	4	1	0	0	90

Figure 4-23

The Number of Cell and Gene Therapies in Different Clinical Trial Phases

Note. Data compiled by the researcher from ClinicalTrials.gov. Retrieved on May 20, 2025. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

In **Figure 4-24** and **Figure 4-25**, the distribution of each therapy across different

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therapeutic areas is presented. The total number of trials of gene therapies currently ongoing has significantly outnumbered that of cell therapies, thanks to CAR-T.

In both gene therapies and cell therapies, the primary focus is on cancer treatment. Generally speaking, cell therapies have a more even distribution across categories, except for cancer. The second highest therapeutic area in gene therapies is immune-related indications. The third is genetic diseases, while it is the second-to-last in the therapeutic areas of cell therapies. Cell therapies tend to focus on diseases related to neurology, psychiatry, or musculoskeletal conditions. The number of indications related to infection, gastrointestinal, endocrine/metabolic, dermatologic, and cardiovascular of cell therapies is also higher than that of gene therapies.

From **Table 4-18**, the number of drugs under clinical trials for each therapy is further categorized by therapeutic area. AAV mainly focuses on genetic and ocular diseases. 85.92% of the trialed CAR-T drugs are related to cancers. CRISPR, as a gene-editing tool, is more widely selected in cancers and genetic diseases, which account for 49.64% and 24.64%, respectively. As for MSC, no area has a percentage exceeding 20%, but a focus on musculoskeletal diseases is observed, accounting for 16.26% of its trials. Similar to CAR-T, 83.14% of the drugs in trials using NK cells are related to cancers. 24.06% of the medicines adopting iPSC are cancer-related, and it is followed by cardiovascular and neurology/psychiatric diseases, each accounting for 14.97% and 13.64%.

In short, focusing on cancer is a common trend in both gene and cell therapies due to its high market potential. However, each therapy has secondary targets based on its unique characteristics.

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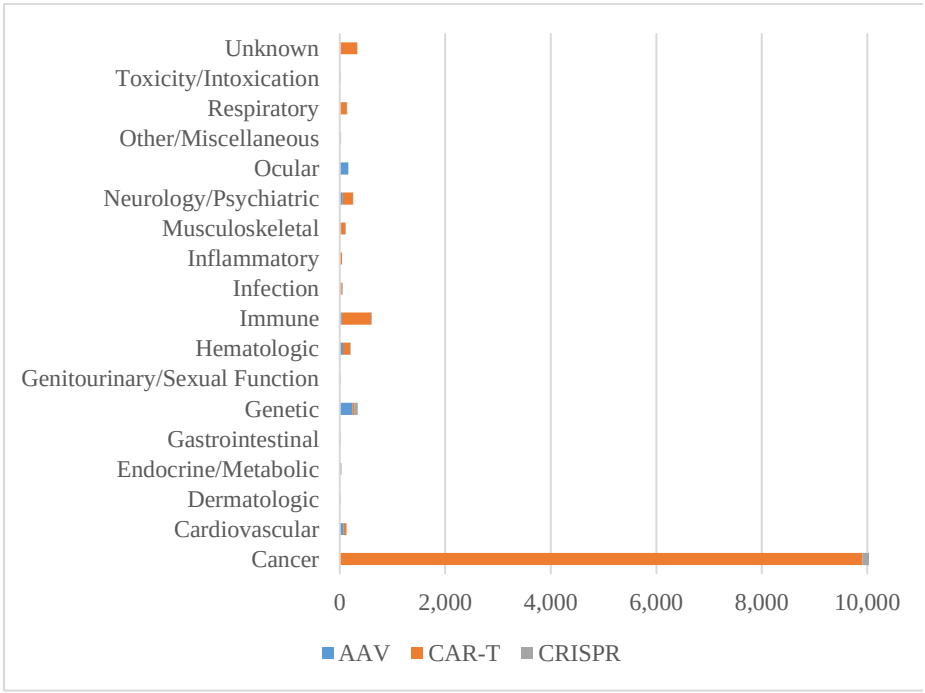

Figure 4-24

Therapeutic Areas of Gene Therapies

Note. Data compiled by the researcher from ClinicalTrials.gov. Retrieved on May 20, 2025. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats.

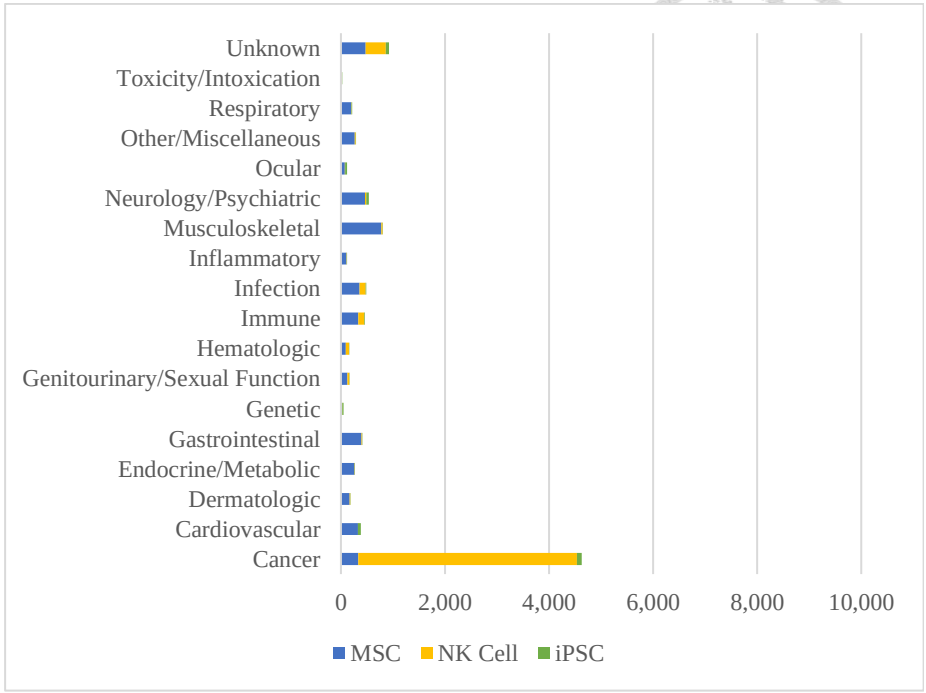

Figure 4-25

Therapeutic Areas of Cell Therapies

Note. Data compiled by the researcher from ClinicalTrials.gov. Retrieved on May 20, 2025. MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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Table 4-18

The Number of Drugs of Cell and Gene Therapies in Different Therapeutic Areas

Therapy Area	AAV		CAR-T		CRISPR		MSC		NK Cell		iPSC	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Cancer	1	0.14%	9,904	85.92%	137	49.64%	332	6.95%	4,205	83.14%	90	24.06%
Cardiovascular	76	10.38%	55	0.48%	0	0.00%	324	6.78%	5	0.10%	56	14.97%
Dermatologic	0	0.00%	13	0.11%	0	0.00%	169	3.54%	11	0.22%	2	0.53%
Endocrine/Metabolic	18	2.46%	1	0.01%	11	3.99%	258	5.40%	3	0.06%	5	1.34%
Gastrointestinal	4	0.55%	12	0.10%	2	0.72%	396	8.28%	12	0.24%	2	0.53%
Genetic	236	32.24%	38	0.33%	68	24.64%	19	0.40%	8	0.16%	22	5.88%
Genitourinary/Sexual Function	3	0.41%	10	0.09%	0	0.00%	122	2.55%	42	0.83%	2	0.53%
Hematologic	60	8.20%	138	1.20%	9	3.26%	96	2.01%	59	1.17%	2	0.53%
Immune	35	4.78%	558	4.84%	13	4.71%	334	6.99%	115	2.27%	12	3.21%
Infection	10	1.37%	29	0.25%	15	5.43%	357	7.47%	120	2.37%	8	2.14%
Inflammatory	20	2.73%	26	0.23%	0	0.00%	107	2.24%	7	0.14%	1	0.27%
Musculoskeletal	23	3.14%	88	0.76%	2	0.72%	777	16.26%	23	0.45%	7	1.87%
Neurology/Psychiatric	58	7.92%	190	1.65%	3	1.09%	465	9.73%	23	0.45%	51	13.64%
Ocular	158	21.58%	0	0.00%	9	3.26%	76	1.59%	4	0.08%	38	10.16%
Other/Miscellaneous	6	0.82%	13	0.11%	1	0.36%	264	5.52%	19	0.38%	1	0.27%
Respiratory	12	1.64%	121	1.05%	4	1.45%	198	4.14%	9	0.18%	12	3.21%
Toxicity/Intoxication	0	0.00%	15	0.13%	0	0.00%	9	0.19%	8	0.16%	1	0.27%
Unknown	12	1.64%	316	2.74%	2	0.72%	477	9.98%	385	7.61%	62	16.58%

Note. Data compiled by the researcher from ClinicalTrials.gov. Retrieved on May 20, 2025. The calculation is based on the indications mentioned; thus, each drug may be calculated more than once if the indications are categorized as different therapeutic areas. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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AAV

Although the statistical data indicate that AAV trials focused more on genetic and ocular diseases, indications categorized as cardiovascular and hematologic diseases also rank high in individual indication comparisons, such as vasculitis, hemophilia A, and hemophilia B. Ocular diseases are primarily associated with macular and retinal degeneration, particularly those that are age-related. Genetic diseases include Duchenne muscular dystrophy, Pompe disease, Spinal muscular atrophy (SMA), etc. Interestingly, many of the high-ranking diseases are genetically ocular ones, such as retinitis pigmentosa and Leber's Congenital Amaurosis.

Compared to the analysis results from Section 4.1.2, the three clusters primarily focused on cancers, nucleic acid sequencing and imaging, and RNA modifications and vaccines. This may suggest that the explorations of AAV in clinical applications are not necessarily identical to those in technology development.

CAR-T

The therapeutic areas of CAR-T are highly focused on one topic: cancer. Lymphomas, leukemias, refractory cancers, lymphoblastic leukemias, myelomas, and other high-ranking cancers are the primary focus of the trialed drugs. Many of the trials are sponsored by institutions in China, including Zhejiang University, Shenzhen Geno-Immune Medical Institute, Chongqing Precision Biotech Co., Ltd., and the Chinese PLA General Hospital. Compared to companies that frequently appear in the CAR-T patent citation network, such as Xencor, the University of Texas System, or Century Therapeutics, they are not the main sponsors or collaborators in the dataset.

The focus of CAR-T, as indicated by the patent citation network, aligns with the statistical results of clinical trials. Besides the patents related to the design of CARs or

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the preparation of immune cells, many of the patents mentioned a specific target that can be linked to certain types of cancer. For example, NO. US11253547B2 describes CD19-directed CARs in immunotherapy (Trager et al., 2022), and NO. US11207349B2 discloses CARs targeting CD19 and CD20 (Yao et al., 2021), which are all related to diffuse large B-cell lymphoma (Gambella et al., 2022). NO. US11827889B2, NO. US11840575B2, and NO. US11351236B2 directly mentions B-cell maturation antigen (BCMA) in their titles (Kochenderfer, 2023; Morgan & Friedman, 2022; Zhang et al., 2023), which is considered the key target of multiple myeloma (Shah et al., 2020). CD7 has been extensively studied as a promising target for CAR-T therapies (Caracciolo et al., 2023). NO. US11440958B2 and NO. US11945865B2 are related to blocking the expression of CD7 (Png et al., 2022, 2024), which may be used for T-cell acute lymphoblastic leukemia (T-ALL) in the future.

CRISPR

Among the clinical trials, CRISPR is primarily used for treating cancers and genetic diseases. The most commonly targeted cancers in the trials are lymphomas, acute myeloid leukemias, and B-cell lymphomas. Genetic diseases are more diverse than cancers, encompassing conditions such as sickle cell diseases, thalassemia, and hemoglobinopathies.

In the patent citation network analysis, two-thirds of the CRISPR clusters are themed around agricultural innovations. The only cluster regarding biotechnology is a web-like structure, where the technological trajectory is still unrecognizable. Almost no patent can be directly linked to specific indications. However, CRISPR Therapeutics AG, being the 22nd primary applicant for CRISPR patents, is ranked first among the sponsors of CRISPR-related clinical trials. This suggests that, although the implementation of

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CRISPR in the clinical field is still under exploration, as reflected in the number of trials, some companies have been working diligently to transform CRISPR from a gene-editing tool into a viable treatment platform.

MSC

Musculoskeletal diseases are the most targeted therapeutic areas among clinical trials that adopt MSCs. The No. 1 indication is arthritis, then followed by osteoarthritis, infectious diseases like coronavirus disease, and diabetes.

Half of the MSC clusters are related to the field, matching the statistical results from the clinical trials. The three clusters are patents surrounding tissue-derived grafts, soft tissue repair, and intervertebral implants. In these technology applications, MSCs are used as the repairing or regenerating cell source or the material for tissue engineering. Thus, the tendency observed in both clinical trial data and patent citation networks is identical.

NK Cell

Similar to CAR-T, the top indications that the clinical trials of NK cells target are lymphomas, leukemias, myelomas, and refractory cancers. The three clusters from the patent citation network of NK cells are related to the improvement of CARs, immune cell therapies, and the protein design of NK cells. “Cancer” is mentioned in several patents, such as NO. US10611814B2, which describes immune cell-based anti-cancer therapeutics, NO. US10072082B2, which discloses immunotherapy that disrupts PD-1/PD-L1 signaling for cancers, and NO. US12098388B2, which provides the production method for NK cells comprising CD56+ (Bachmann & Ehninger, 2020; Cogswell et al., 2018; S. W. Park et al., 2024).

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iPSC

The indications included in the clinical trials of iPSCs are diverse, with no single indication accounting for more than 10 drugs being experimented on. Some indications that rank higher include heart failure, Parkinson's disease, amyotrophic lateral sclerosis, and cardiomyopathy, among others, covering various therapeutic areas. The two clusters of iPSC center on iPSC-based cell engineering, genome editing platforms, and iPSC-derived platelets. Some patents may describe a technology that can be linked to a specific indication, but the tendency to implement the technology remains vague. For example, patent NO. US11767507B2 mentioned GABAergic, which is related to neurodegenerative diseases, and NO. US10894065B2 provides methods for producing platelets from pluripotent stem cells (Chung, 2023; Feng et al., 2021). The gap between technology development and real-world clinical usage still requires more resources and engagement to overcome.

4.1.4 The Strategic Group of CGTs

From the conclusion drawn from section 0, considering yearly incremental numbers of patent applications and the distributions by sectors, the six modalities can be roughly categorized into the following groups:

- Technology matured, commercially under development: MSC
- Technology close to maturity, commercial growth highly driven by SMEs: CRISPR
- Growing technology and commercially recognized (big pharma engaging): CAR-T, NK cell
- Technology is likely to mature, and the academic sector is dominating: AAV, iPSC

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Clinical trials and the formation of patent trajectories are also added as analytic factors in the discussion of sections 4.1.2 and 4.1.3.

- AAV focuses differently between patent citation clusters and clinical trials. A patent trajectory forming in the cluster (a), which is the central cluster, indicates that the technological development of AAV has reached a certain extent of maturity.
- CAR-T is the only modality that has formed a complete trajectory across the integrated citation network, and the clinical focus aligns with the current clinical development.
- In the CRISPR citation network, only the cluster (d) is related to medicine, yet no trajectory is found. The limited number of clinical trials suggests that the implementation of CRISPR into clinical practices is still being explored, as concerns about the ethics of gene editing and the unknown risks are hindering researchers.
- MSC, the modality with the most clusters in its citation network, demonstrates a highly similar trend in the therapeutic areas that both patents and trials are focusing on.
- The NK cells' citation network observation shows that the technology is still under development due to the lack of trajectory formation. The main cluster (n) approximately matches the clinical indication of the trials.
- From the perspective of patent citation network analysis, iPSC is close to maturity, as trajectories can be observed in both clusters (one central and one minor). However, the links between the patent focus and trials' therapeutic areas remain weak, indicating a clinical exploration stage.

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To incorporate the above analytical factors into a single system, the method of strategic groups is employed. Two indicators are adopted: the number of clinical trials that have entered phase II and the development stages of the patent trajectory.

The development stage of each CGT modality along the patent trajectory axis was determined based on citation network structure, following a five-stage classification scheme (see **Table 4-19**). In this scheme, technologies with multiple disconnected clusters (Stage 1) reflect early fragmentation, while a consolidated citation structure with an observable trajectory (Stage 5) indicates technological maturity and centralization. This method captures not only the quantity but also the structural cohesion of innovation.

Table 4-19

The Criteria for the Different Development Stages of Technology

Stage	Criteria
1	More than three clusters in the citation network without distinction
2	Less than three clusters in the citation network, with a distinction between primary and secondaries, but no patent trajectory found
3	Less than three clusters in the citation network, with a patent trajectory found in the main cluster
4	Only one cluster in the citation network
5	Only one cluster in the citation network, with a patent trajectory observable

Note. Compiled by the researcher. The number of clusters in the citation network and the formation of the patent trajectory is considered.

The six CGT modalities are thereby divided into three strategic groups as shown in **Figure 4-26**, revealing their respective stages of technological maturity and clinical translation, which is highly relevant to commercial activities:

- Group A: MSC stands alone as a technology with extensive clinical penetration but a fragmented or stagnant patent structure. Despite its low

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position on the patent maturity scale, MSC has entered over 900 Phase II trials, indicating that it is a clinically validated and widely tested modality. This suggests a trajectory driven more by practical therapeutic application and regenerative medicine practices than by recent technological innovation. This also aligns with the distribution of patent applicants, where no sector dominates the technology.

However, without a dominating technology, it also means that there are fewer possibilities for MSC to have greater economic scale and scope, even though it is already adopted in clinical applications.

- Group B: CAR-T represents the opposite end of the spectrum. It has achieved high maturity in both patent trajectory and clinical development, placing it in a strategic sweet spot. The field benefits from technological consolidation (patent trajectory Stage 5), significant clinical trial activity, and the active involvement of commercial and hybrid institutional actors. This positioning highlights CAR-T as a model for the industrialization and translational success of CGT, and has become the industrial standard.
- Group C: The remaining modalities, including CRISPR, AAV, iPSC, and NK cell therapy, form a third cluster characterized by early- to mid-stage patent development and relatively low to moderate clinical validation. Although they vary in technical trajectories (e.g., iPSC and AAV are closer to Stage 3, CRISPR and NK closer to Stage 1-2), these modalities share a typical profile of emerging or evolving innovation. Their large patent volumes suggest intense R&D activity, but limited clinical penetration points to ongoing translational challenges, regulatory

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uncertainty, or technological fragmentation. These technologies may benefit from focused efforts in platform optimization, safety validation, or strategic partnerships to accelerate their clinical readiness.

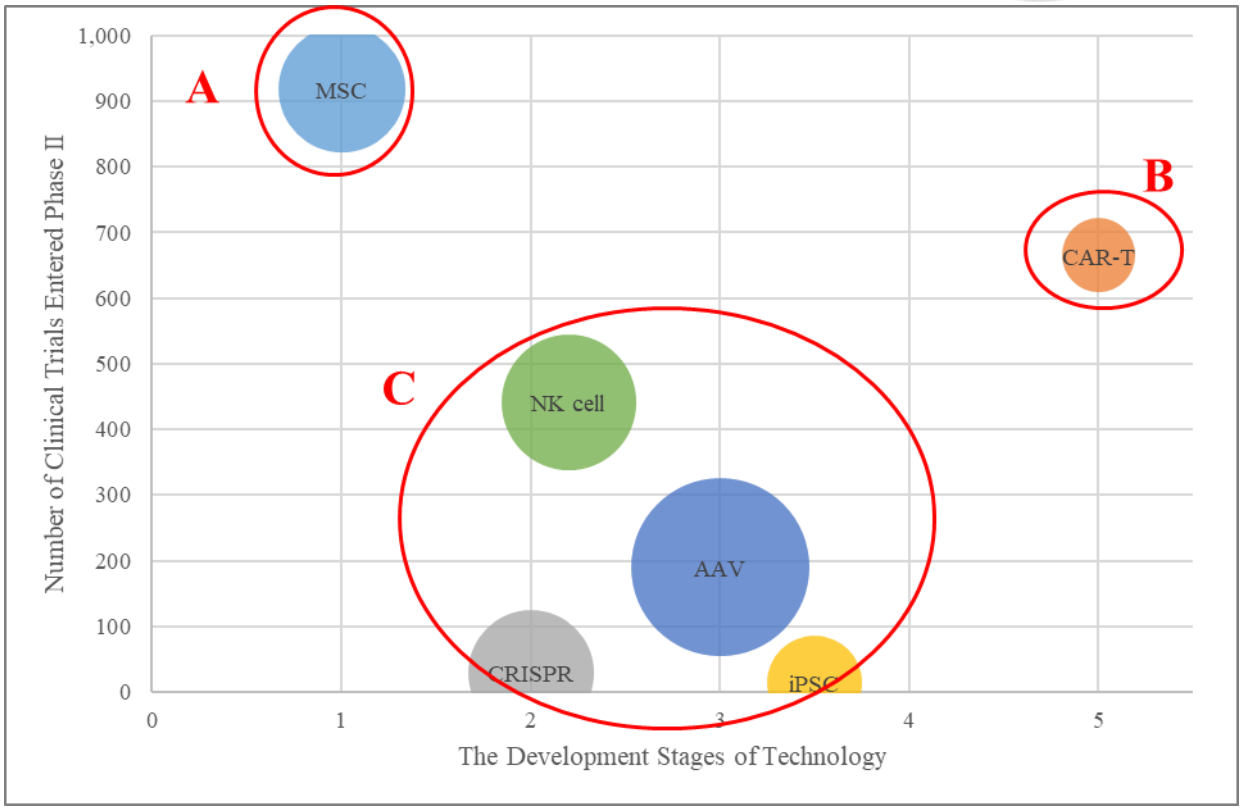

Figure 4-26

Strategic Grouping of Cell and Gene Therapies Modalities Based on Patent and Clinical Maturity

Note. Compiled by the researcher. The development stages of the patent trajectory are illustrated in **Table 4-19**. The size of the circle represents the total number of patents (1976-2024) of each modality. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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In summary, the features of each group can be concluded in **Table 4-20**.

Table 4-20

Strategic Grouping of Cell and Gene Therapies Modalities Based on Patent Trajectory and Clinical Development Features

Group	Features	Example
A	• Stagnant (long-developed but no trajectory formation) or fragmented technology development (many clusters found in the network) • High number of clinical trials, indicating a practice-led growth • Absence of a dominant sector or coordinated innovation push	MSC
B	• Consolidated and mature patent trajectory • Clinically recognized with multiple trials in advanced stages • Increasing involvement by major pharmaceutical firms	CAR-T
C	• Technology trajectory under development (e.g., NK cell, CRISPR) • Little to moderate number of clinical trials (e.g., CRISPR, iPSC, AAV) • Misalignment between patenting activities and clinical applications (e.g., iPSC, AAV) • Academic as the leading sector (e.g., AAV, iPSC), or no signs of large pharmaceutical proactively involved (e.g., CIRSPR, iPSC)	NK cell, AAV, CRISPR, iPSC

Note. Compiled by the researcher. AAV=adeno-associated virus; CAR-T=chimeric antigen receptor T-cell; CRISPR=clustered regularly interspaced short palindromic repeats; MSC=mesenchymal stem cell; NK Cell=natural killer cell; iPSC=induced pluripotent stem cell.

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4.2 The Landscape of CGT Approvals and Pricing: Case Study of the US, EU, and Japan

4.2.1 Current Approved CGTs and Their Prices

One of the problems CGTs are facing now is the discrepancies in regulations among different countries. A report by Aitken et al. (2024) illustrated the current regulatory frameworks of several countries. Most developed countries have established a dedicated authority for regulating and examining CGTs, also referred to as regenerative therapies in regulatory terminology.

The different regulatory systems and approval pathways will significantly impact the development of CGT in a country. In this study, the United States, the European Union, and Japan are selected for discussion of their different approaches to regulating CGTs.

United States

Table 4-21 presents compiled data of the authorized CGTs from 2011 to 2024 in the US. Among the 44 CGTs, 32 were granted at least one expedited pathway (72.73%). There are five expedited designations. 65.91% were granted Orphan designation, 36.36% were granted Breakthrough therapy designation, 31.82% were granted Fast track, 29.55% were granted Regenerative Medicine Advanced Therapy Designation (RMAT), and 15.91% were granted rare pediatric disease designation. The frequent use of expedited programs underscores the FDA's commitment to accelerating patient access to innovative therapies in areas of high unmet medical need, a conclusion that Tandulje et al. (2025) have also drawn from their studies.

1. Orphan Product Designation

   This designation can be granted to drugs or biologics aimed at preventing,

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diagnosing, or treating rare conditions. It offers sponsors incentives like tax credits for clinical trials, waived user fees, and seven years of market exclusivity after approval. This means that manufacturers can use this strategy to extend their exclusivity in the market by adding new, rare indications. For example, Yescarta and Breyanzi have both extended their exclusivity to 2029 and 2031, respectively, by exclusivity-protected indications. However, orphan designation is separate from the approval process, and designated drugs must still undergo the same rigorous FDA review as other treatments (US FDA, 2024a).

2. Breakthrough Therapy Designation

   To qualify, a drug must show initial clinical evidence indicating significant improvements over current treatments on important clinical endpoints. The determination of "substantial improvement" involves professional judgment based on the magnitude and duration of the treatment effect, as well as the importance of the clinical outcome. Qualifying endpoints typically include those measuring irreversible morbidity or mortality (IMM), severe disease-related symptoms, or validated surrogate and intermediate endpoints. Improvements in safety profiles may also be considered if comparable efficacy is demonstrated (US FDA, 2018).

   Drugs granted Breakthrough Therapy Designation can benefit from all Fast Track features, along with intensive FDA guidance that begins in the early development stages, often starting in Phase I. Additional advantages include greater organizational support and frequent interactions with senior FDA reviewers to optimize development plans (US FDA, 2018).

3. Fast Track Designation

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The Fast Track program is designed to speed up the development and review of drugs or biologics that meet two key criteria:

- They are designed for treating serious or life-threatening conditions, and
- They demonstrate the potential to meet unmet medical needs.

Sponsors usually request Fast Track designation during the Investigational New Drug (IND) stage of development (US FDA, 2025b).

4. Regenerative Medicine Advanced Therapy (RMAT) Designation

   The designation was created to speed up the development and review of regenerative therapies for serious or life-threatening conditions. To qualify, a product must meet three main criteria. First, it must be classified as a regenerative medicine therapy, including cell therapies, therapeutic tissue-engineered products, human cell and tissue products, or relevant combination products. Second, the therapy must aim to treat, modify, reverse, or cure a serious or life-threatening disease or condition. Third, there must be preliminary clinical evidence showing the product's potential to meet unmet medical needs in that context. The FDA also considers this definition to include certain human gene therapies and xenogeneic cell products, potentially (US FDA, 2023b).

5. Rare Pediatric Disease Designation

   The FDA's Rare Pediatric Disease Priority Review Voucher (PRV) program incentivizes drug development for rare diseases affecting children. Under this program, sponsors who receive FDA approval for qualifying drugs or biologics may be awarded a voucher that can be:

   - Redeemed to obtain priority review for a different product, or

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- Transferred or sold to another sponsor.

However, as per the Continuing Appropriations and Extensions Act, 2025, the PRV program will begin to sunset after December 20, 2024 (US FDA, 2024b).

Aitken et al. (2024) have made similar observations, noting that approved CGTs commonly utilize certain expedited pathways and are more widely accepted in the early stages.

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Table 4-21

The List of Approved Cell and Gene Therapies in the United States (2011-2024)

Year of Approval	Name of The Product	Approval Designation	Therapeutic Area	List Price
2011	Laviv		Nasolabial fold wrinkles	$475,000[A,B,C]
2011	Hemacord (HPC, cord blood)		Hematologic disorders	
2011	HPC, Cord Blood - Bloodworks		Hematologic disorders	
2012	Ducord, HPC Cord Blood		Hematologic disorders	
2012	Gintuit		Mucogingival conditions	
2012	HPC, Cord Blood		Hematologic disorders	
2013	HPC, Cord Blood - LifeSouth		Hematologic disorders	
2015	Imlygic	Fast track, Orphan	Recurrent melanoma	$65,000[B]
2016	Clevecord (HPC Cord Blood)		Hematologic disorders	
2017	Kymriah	Orphan, Breakthrough	Follicular lymphoma, acute lymphoblastic leukemia, diffuse large B-cell lymphoma	$57,000[G]
2017	Luxturna	Orphan, Breakthrough	Biallelic RPE65 mutation-associated retinal dystrophy	$425,000/eye[C] $850,000[B] $1,020,000[G]

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Table 4-21 (continued)

Year of Approval	Name of The Product	Approval Designation	Therapeutic Area	List Price
2017	Maci	Orphan	Growth hormone deficiency, pulmonary arterial hypertension	$28,650[G]
2017	Yescarta	Orphan, Breakthrough	Follicular lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma	$373,000[B,C] $447,600[G]
2018	HPC, Cord Blood - MD Anderson Cord Blood Bank		Hematologic disorders	
2019	Allocord (HPC, Cord Blood)		Hematologic disorders	
2019	Provenge		Metastatic castrate resistant (hormone-refractory) prostate cancer	$169,206[G]
2019	Zolgensma	Fast track, Orphan, Breakthrough, Pediatric	Spinal muscular atrophy	$2,000,000-$2,125,000[B,C]
2020	Tecartus	Orphan, Breakthrough	Lymphoma, leukemia	$373,000[B,C]
2021	Abecma	Breakthrough, Fast track, Orphan	Multiple myeloma	$419,500[B,D]
2021	Breyanzi	Orphan, Breakthrough, RMAT	Lymphoma, leukemia	$410,300[B]
2021	Rethymic	Fast track, Breakthrough, RMAT, Pediatric, Orphan	Arrhythmia	
2022	Adstiladrin	Breakthrough, Fast track	Bladder cancer	

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Table 4-21 (continued)

Year of Approval	Name of The Product	Approval Designation	Therapeutic Area	List Price
2022	Skysona	Orphan, Breakthrough, Pediatric	Cerebral adrenoleukodystrophy (cald)	
2022	Stratagraft	Orphan, RMAT	Deep-partial thickness burns	
2022	Zynteglo	Fast track, Orphan, Breakthrough, Pediatric	Beta thalassemia	$280,000[B,C]
2022	Carvykti	Orphan, Breakthrough	Multiple myeloma	
2022	Hemgenix	Orphan, Breakthrough	Haemophilia B	
2023	Casgevy	Fast track, Orphan, RMAT	Sickle-cell disease, Beta-thalassemia	$2,200,000[D,E]
2023	Lantidra	Orphan	Type 1 diabetes	$300,000[D]
2023	Lyfgenia	Fast track, Orphan, RMAT, Pediatric	Sickle-cell disease	$3,100,000[E]
2023	Omisirge	Breakthrough, Orphan	Hematologic malignancies	
2023	Roctavian	Fast track, Orphan, Breakthrough, RMAT	Hemophilia A	$2,900,000[F]
2023	Vyjuvek	Orphan, Fast track, RMAT, Pediatric	Wounds, Epidermolysis bullosa	
2024	Amtagvi	Fast track, Orphan, RMAT	Melanoma	
2024	Aucatzyl	RMAT, Orphan	B-cell precursor acute lymphoblastic leukemia (ALL)	

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Table 4-21 (continued)

Year of Approval	Name of The Product	Approval Designation	Therapeutic Area	List Price
2024	Beqvez	Orphan, Breakthrough, RMAT	Hemophilia B	
2024	Elevidys	Fast track, Orphan	Muscular dystrophy	
2024	Kebilidi	Orphan	Aromatic L-amino acid decarboxylase (AADC) deficiency	
2024	Lenmeldy	Orphan, Pediatric, RMAT	Leukodystrophy	
2024	Ryoncil	Fast track, Orphan	Steroid-refractory acute graft versus host disease (SR-agvhd)	
2024	Symvess	RMAT	Vascular conduit for extremity arterial injury	
2024	Tecelra	Orphan, RMAT	Sarcoma	
2024	Regenecyte (HPC, Cord Blood)		Hematologic disorders	

Note. Compiled by the researcher from the US FDA. RMAT = Regenerative Medicine Advanced Therapy Designation. HPC = hematopoietic progenitor cell.

Sources: [A] from Bach et al. (2017). [B] from Horrow and Kesselheim (2023). [C] from Wong et al. (2023). [D] from Zhang and Shugarman (2024). [E] from Conti et al. (2025). [F] from Zemplenyi et al. (2024). [G] from Shukla et al. (2019).

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European Union

According to the EMA's list of approved medicines (see **Table 4-22**), several pathways are frequently used for CGTs.

To promote the welfare of minority patients and encourage applicants to develop pharmaceutical products for them, several special "labels" are created for applicants, and incentives or special marketing authorization (MA) are designed for those applicants who are eligible. For example, PUMA (Paediatric Use Marketing Authorisation) benefits from an 8+2-year period of data and market protection. Conditional MA is granted for products that address unmet needs, and MA under exceptional circumstances is granted to applicants who cannot provide comprehensive data on efficacy and safety.

Five special MAs have been utilized by CGTs in the EU:

1. Accelerated assessment

   Accelerated assessment shortens the EMA's standard review period for marketing authorization applications from 210 to 150 days (excluding clock stops), provided the product is deemed of major public health interest and represents significant therapeutic innovation. To qualify, applicants must justify the product's relevance to public health and its innovative potential. The application must also include details on Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) compliance, enabling the EMA to integrate necessary inspections into the accelerated review timeline (EMA, n.d.-a).

2. PRIME

   The EMA established the PRIority MEdicines (PRIME) scheme to provide early and proactive regulatory support for medicines addressing unmet medical needs. PRIME facilitates the generation of high-quality data on a

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medicine's benefits and risks, thereby accelerating patient access to potentially transformative therapies (EMA, n.d.-f).

Building on existing tools, such as scientific advice and accelerated assessment, PRIME offers enhanced, stage-specific support throughout the development process. Key features include early appointment of rapporteurs, kick-off meetings with multidisciplinary EMA experts, a dedicated scientific coordinator, iterative and expedited scientific advice, and submission readiness meetings. These interactions help streamline clinical development, ensure an appropriate trial design, and increase the likelihood of a successful and timely marketing authorization (EMA, n.d.-f).

Medicines in the PRIME scheme are expected to be eligible for accelerated assessment at the time of application. Updates introduced in March 2023, based on a five-year program review, have further strengthened EMA's support measures, improving coordination and flexibility for developers navigating the regulatory process (EMA, n.d.-f).

3. Orphan designation

The EU provides various incentives to encourage the development of orphan medicines. Sponsors with orphan designation benefit from protocol assistance—specialized scientific guidance for rare diseases, as well as market exclusivity once approved. They can also receive reductions in regulatory fees, which depend on the sponsor's status and the specific service requested. Notably, since June 19, 2020, academic researchers developing orphan drugs have been eligible to receive protocol assistance at no cost, further encouraging innovation in educational and non-commercial settings (EMA, n.d.-d).

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4. Conditional marketing authorization

   To address unmet medical needs, the EMA may grant conditional marketing authorization based on less comprehensive data when early access is deemed to outweigh the uncertainties. This applies to medicines for serious or life-threatening conditions, including orphan drugs, as well as those intended for public health emergencies, such as pandemics. In such cases, streamlined clinical, pharmaceutical, and non-clinical data may be accepted. The legal basis is Article 14-a of Regulation (EC) No. 726/2004 (EMA, n.d.-b).

   The Conditional MA is valid for only one year and is renewable annually (EMA, n.d.-e).

5. Exceptional circumstances

   Marketing authorization is granted in exceptional cases, as described in Article 14(8) of Regulation (EC) No 726/2004, with further details provided in Part II of Annex I of Directive 2001/83/EC. This pathway is used when an applicant cannot provide complete data on efficacy and safety under normal use circumstances, due to the rarity of the condition, limited scientific knowledge, or ethical constraints that restrict data collection. In such cases, authorization is conditional upon the implementation of specific measures, including enhanced safety monitoring, mandatory incident reporting, and other risk management actions as required by the relevant authorities. The product will be reviewed annually to reevaluate the risk-benefit balance (EMA, n.d.-e). However, an MA under exceptional circumstances will not typically result in a regular MA under usual circumstances. On the other hand, conditional MA is possible (EMA, n.d.-e).

Of the 27 CGTs, only five were not involved in any special designations. All

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applications submitted after 2018 have been processed through accelerated pathways. Orphan designation is the most commonly used pathway, accounting for 20 CGTs (74.07%); the second most common is PRIME (14 CGTs, accounting for 51.85%), followed by conditional MA (33.33%).

The pricing and reimbursement (P&R) criteria are highly diverse in the EU. For example, the P&R of Germany begins by categorizing ATMPs as either a medicine or a medical procedure, which leads to different regulatory units for further evaluation (Ronco et al., 2021). On the other hand, the UK separates the ATMPs according to their indication, whether it is for a rare disease or not, which falls into different HTA processes for evaluation (Ronco et al., 2021). Nonetheless, to date, only CAR-T has a more widely recognized reimbursement across the EU5 countries (Italy, the UK, France, Germany, Spain).

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Table 4-22

The List of Approved Cell and Gene Therapies in the European Union (2009-2024)

Year of Approval	Product Name	Approval Designation	Indication	Reimbursed Price	($)	List Price
2009	ChondroCelect[#]		Cartilage Diseases			$24,000 (UK)[A]
2012	Glybera[#]	Orphan	Hyperlipoproteinemia Type I			$1,398,321 (Germany)[A]
2013	MACI[#]		Fractures, Cartilage			$21,000 (UK)[A]
2013	Provenge[#]		Prostatic Neoplasms			€79,953 (Germany)[D] $61,500 (EU)[A]
2015	Holoclar	Orphan	Stem Cell Transplantation; Corneal Diseases	€95,000 (Italy)[B,i] €88,993*/eye (UK)[B]	103,550 - 194,005	$105.000 (UK)[A]
2015	Imlygic		Melanoma	€1,858*/vial (UK)[B]	2,025/vial	$316,245 (Germany)[A] €72,288-€289,151 (Germany)[E]
2016	Strimvelis	Orphan	Severe Combined Immunodeficiency	€ 594,000 (Italy, UK)[B,i]	647,460	$690,000 (EU)[A]
2016	Zalmoxis[#]	Orphan, Conditional approval	Hematopoietic Stem Cell Transplantation; Graft vs Host Disease	€149,000 (Italy)[B,vi] €130,000 (Germany)[B]	141,700 - 162,410	$844,383 (Italy)[A] $928,821 (Germany)[A]
2017	Spherox		Cartilage Diseases	€11,124* (UK)[B]	12,125	$9,000-12,000 (EU)[A]
2018	Alofisel[#]	Orphan	Rectal Fistula	€95,000 (Germany)[D,i] €54,000 (France)[B] €60,000 (Germany)[B] €60,000/treatment (Spain)[B]	58,860 - 103,550	$70,632 (UK)[A]
2018	Yescarta	Orphan, PRIME	Lymphoma, Follicular; Lymphoma, Large B-Cell, Diffuse	€327,000 (France)[B] €327,000 (Germany, Italy, Spain)[B,C,i] €317,000/£282,451 (UK)[C]	345,530 - 356,430	

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Table 4-22 (continued)

Year of Approval	Product Name	Approval Designation	Indication	Reimbursed Price	($)	List Price
2018	Kymriah	Orphan, PRIME	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma; Lymphoma, Large B-Cell, Diffuse	€320,000 (Germany)[B,C,i] £282,000 (UK)[C,D] €320,000 (Italy, Spain, Germany)[B,i] €313,766* (UK)[B] €297,666+15,000 (France)[B]	340,806 – 348,800	$416,481 (Germany)[A] $364,948 (UK)[A] $371,000 (Switzerland)[A]
2018	Luxturna	Orphan	Leber Congenital Amaurosis; Retinitis Pigmentosa	€360,000 (Denmark)[B,C] €341,000 (UK)[C] €682,673* (UK)[B] €345,000 (Germany)[B,C] €345,000 (Spain)[C,iii] €360,000 (Italy)[C,iii] €290,000 (France)[C]	316,100 – 744,114	
2019	Zynteglo[#]	Orphan, PRIME, Accelerated assessment, Conditional approval	beta-Thalassemia	€1,580,000 (Germany)[B,v]	1,722,200	
2020	Zolgensma	Orphan, PRIME, Conditional approval	Muscular Atrophy, Spinal	€3,210,000 (Italy)[C,i] €2,325,000 (Germany)[C,i] £1,795,000 (UK)[C]	2,323,694 – 3,498,900	
2020	Libmeldy	Orphan	Leukodystrophy, Metachromatic	€2,875,000 (Germany, UK)[D]	3,133,750	
2020	Tecartus	Orphan, PRIME, Conditional approval	Lymphoma, Mantle-Cell	€360,000 (Germany)[D]	392,400	
2021	Skysona[#]	Orphan, PRIME	Adrenoleukodystrophy			
2021	Abecma	Orphan, PRIME	Multiple Myeloma	€350,000 (Germany)[D]	381,500	
2022	Breyanzi	PRIME	Lymphoma, Large B-Cell, Diffuse; Lymphoma, Follicular; Mediastinal Neoplasms	€345,000 (EU)[D]	376,050	

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Table 4-22 (continued)

Year of Approval	Product Name	Approval Designation	Indication	Reimbursed Price	($)	List Price
2022	Carvykti	Orphan, PRIME, Conditional approval	Multiple Myeloma			$465,000 [E]
2022	Upstaza	Orphan, Exceptional circumstances	Amino Acid Metabolism, Inborn Errors	€4,165,000/3,500,000 (Germany)[D]	3,815,000 – 4,539,850	
2022	Roctavian	Orphan, PRIME, Conditional approval		€2,143,960 (Germany)[D]	2,336,916	
2022	Ebvallo	Orphan, PRIME, Exceptional circumstances	Lymphoproliferative Disorders			
2023	Hemgenix	Orphan, PRIME, Conditional approval	Hemophilia B			
2024	Casgevy	Orphan, PRIME, Conditional approval	beta-Thalassemia; Anemia, Sickle Cell	€1,900,000 (France)[D]	2,071,000	
2024	Beqvez[#]	PRIME, Conditional approval	Hemophilia B			

Note. Compiled by the researcher from the European Medicines Agency. QALY= Quality-Adjusted Life Year; PRIME = PRIority Medicines.

[#] represents expired, withdrawn, or not-renewed MA; * represents hidden discount excluded. [i] means an outcome-based payment is adopted (payment by result); [ii] means authorized temporary use; [iii] means payment with a ceiling cap; [iv] means the price is compared to a conventional treatment or caring services; [v] means prepayment and yearly outcome-based payments; [vi] means flat price per patient.

Sources: [A] from Shukla et al. (2019). [B] from Ronco et al. (2021). [C] from Lee and Lee (2023). [D] from Mahalatchimy et al. (2024). [E] from Dennis (2022).

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Japan

The approved CGTs over the past ten years are listed in **Table 4-23**. There were 20 kinds of CGTs approved in total; only two of them did not use any expedited program.

Five CGTs are conditional time-limited approvals, including HeartSheet, Stemirac, Delytact, Collategene, and Akuugo.

There are three expedited pathways applicants can use to apply for CGTs market approval in Japan.

1. Orphan drugs

   For the application for orphan drug designation, applicants benefit from priority review and consultation, even if the orphan indication is just one of the overall target diseases. Suppose an orphan drug is not initially considered subject to priority review/consultation at the time of designation, but later fulfills the criteria as development progresses. In that case, the applicant can utilize the consultation service of the PMDA to clarify their eligibility (MHLW, 2024a, 2024b).

2. SAKIGAKE

   On June 17, 2014, Japan's MHLW introduced the "SAKIGAKE Strategy", aiming to position the country at the forefront of global innovation in medical product development and application. This comprehensive initiative spans the entire spectrum of the medical innovation pipeline, from basic and clinical research to regulatory review, safety monitoring, insurance reimbursement, infrastructure development, support for corporate activity, and facilitation of global market entry (PMDA, n.d.).

   It consists of two measurements: the SAKIGAKE Designation System and the Scheme for Rapid Authorization of Unapproved Drugs, which

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accelerates the practical use of investigational or off-label therapies in managing severe and life-threatening conditions (MHLW, n.d.-a). This system is similar to the “Breakthrough Therapy Designation System” launched by the US in 2012 and PRIME, initiated by the EU (Maruyama et al., 2018).

3. Conditional & Time-limited Approval

   Under this pathway, applicants only need to submit an estimate of efficacy and ensure safety for the collection of clinical data, thereby allowing products to reach the market more quickly. For the CGTs that were granted “Conditional & Time-limited Approval”, they need to reapply within the specified period, or their conditional & time-limited approval will expire (Maruyama, 2024). The pathway, compared to the conventional one, is displayed in **Figure 4-27**.

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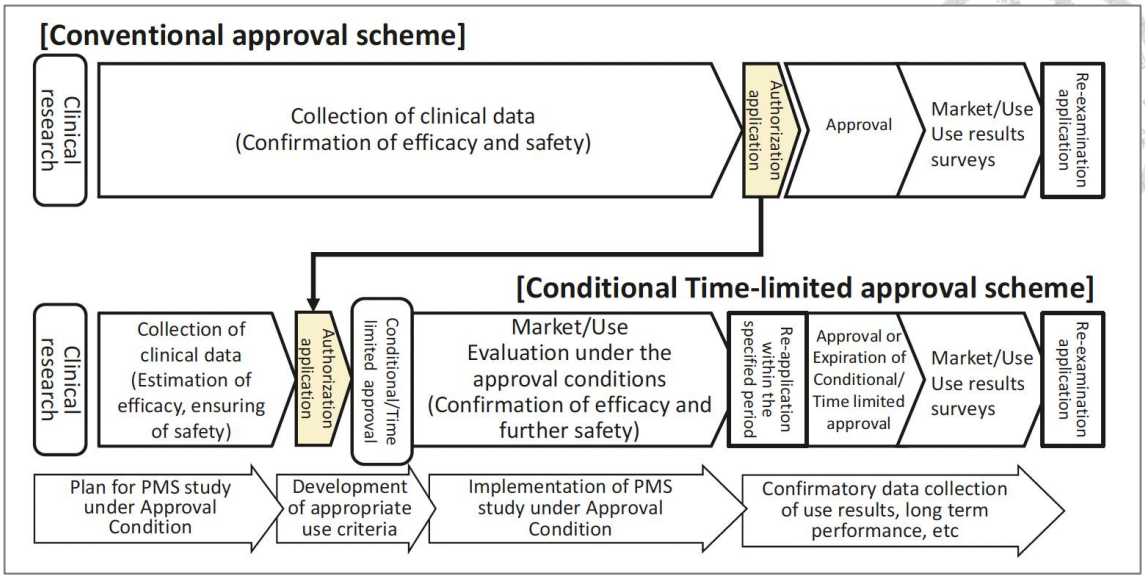

Figure 4-27

The Approval Schemes of Regenerative Medical Products Include Conventional Approval and Conditional Time-Limited Approval in Japan

Note. Reprinted with permission from "Regulatory Aspects of Cell and Gene Therapy Products: The Japanese Perspective" by Yoshiaki Maruyama, Shinichi Noda, Shinichi Okudaira et al, 2023, "Regulatory Aspects of Gene Therapy and Cell Therapy Products. Advances in Experimental Medicine and Biology", vol. 1430. (https://doi.org/10.1007/978-3-031-34567-8_9). Copyright 2023, The Author(s), under exclusive license to Springer Nature Switzerland AG.

Of the 20 CGTs, 80% used the orphan drugs designation, 25% used Conditional & Time-limited Approval, and 20% used SAKIGAKE.

MHLW determines the health insurance coverage and pricing after consulting with the Central Social Insurance Medical Council (Chu-I-Kyo). If a new drug is considered similar in method, the price of the new drug is determined by the one-day expenditure of the similar drug (Fukuda, 2018).

Nine CGTs are reimbursed by MHLW, including Stemira, Kymriah, Zolgensma,

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Alofisel, Breyanzi, Delytact, Yescarta, Abecma, and Luxturna. Four of them are CAR-T therapies (Kymriah, Yescarta, Breyanzi, Abecma), which were priced the same; two are AAV therapies (Zolgensma, Luxturna), which were the two highest; and one is an MSC therapy (Stemira).

As for the therapeutic areas they cover, oncology-related are the most numerous, accounting for six, followed by ophthalmologic diseases, which account for five.

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Table 4-23

The List of Approved CGTs in Japan (2015-2024)

Year of Approval	Product Name	Approval Designation	Indication	Reimbursed Price (¥) *	($)***
2015	Heartsheet	Conditional/Time-limited Approval	Heart failure		
2015	Temcell	Orphan	Acute graft-versus-host disease		7,248[a]
2016	Jace**	Orphan	Severe and extensive burns, giant congenital melanocytic nevus		
2018	Stemirac	SAKIGAKE, Conditional/Time-limited Approval	Neurological symptoms and functional disorders associated with spinal cord injury	15,234,750	102,073
2019	Collategene	Conditional/Time-limited Approval	Ulcers associated with chronic arterial occlusion		
2019	Kymriah**	Orphan	CD-19-positive B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma	32,647,761	218,740
2020	Nepic	Orphan	Limbal stem cell deficiency		
2020	Zolgensma	Orphan, SAKIGAKE	Spinal muscular atrophy	167,077,222	1,119,417
2021	Alofisel	Orphan	Complex perianal fistula disease	5,620,004	37,654
2021	Breyanzi**	Orphan	Large B-cell lymphoma and Follicular lymphoma	32,647,761	218,740
2021	Delytact	Orphan, SAKIGAKE, Conditional/Time-limited Approval	Malignant glioma	1,431,918	9,594
2021	Ocural	Orphan	Corneal epithelium defects		
2021	Yescarta**	Orphan	Large B-cell lymphoma	32,647,761	218,740
2022	Abecma**	Orphan	Multiple myeloma	32,647,761	218,740
2022	Carvykti	Orphan	Multiple myeloma		

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Table 4-23 (continued)

Year of Approval	Product Name	Approval Designation	Indication	Reimbursed Price (¥) *	($)***
2022	Sakracy	Orphan	Limbal stem cell deficiency		
2023	Jacemin		Transplantation for vitiligo		
2023	Luxturna	Orphan	Inherited retinal dystrophy	49,600,226	332,322
2023	Vyznova	Orphan	Damaged corneal endothelial monolayer tissue		
2024	Akuugo	Orphan, SAKIGAKE, Conditional/Time-limited Approval	Chronic motor paresis associated with traumatic brain injury		

Note. Compiled by the researcher from the Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labour and Welfare (MHLW). * represents announcement from MHLW. The price validation is scheduled for March 31, 2025. ** represents that there are multiple application records; the earliest approved time will be used in this table. *** ¥1 = $0.0067.

Source: [a] From Shukla et al. (2019)

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4.2.2 The Analysis of the Approved CGTs and Their Prices of The Three Systems

As discussed in section 4.2.1, a common characteristic of regulatory systems is that they offer multiple expedited designations, and most products utilize more than one designation.

There are 66 CGTs that the US, EU, and Japan have approved, including 32 gene therapies (18 *ex vivo* and 14 *in vivo*) and 34 cell therapies (20 allogeneic and 14 autologous).

Table 4-24 compares the number of approved CGTs across the US, EU, and Japan from 2009 to 2024, categorized by product type, source (autologous vs. allogeneic), and delivery method (*in vivo* vs. *ex vivo*). The data highlights striking differences in regulatory behavior and health system responsiveness among the three regions.

The US approved a total of 44 CGT products, significantly outpacing the EU (27) and Japan (20), suggesting a more permissive or accelerated regulatory environment, especially in areas such as CAR-T therapies and *in vivo* AAV-based gene therapies. Due to the fragmented nature of the US's system, its reimbursement data could not be gathered thoroughly; thus, it is not displayed in the table.

In contrast, despite the EU having a significant variety of reimbursements across the region, 23 out of 27 (approximately 85%) approved products were found to have reimbursement records. This suggests that, although reimbursement decisions in the EU are made independently by national health authorities, the high proportion of authorized CGTs being reimbursed indicates a degree of convergence or policy alignment across member states.

Japan, despite a smaller absolute number of approvals (20), demonstrates a stricter gatekeeping mechanism, with only nine products reimbursed, representing 45% of those

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approved.

In terms of product characteristics, *ex vivo* autologous gene therapies are the most commonly approved subtype across all regions, reflecting the clinical maturity of CAR-T and hematopoietic stem cell modification platforms. *In vivo* gene therapies are also experiencing substantial growth, particularly in the US and EU, where AAV-based products, such as Zolgensma, Luxturna, and Hemgenix, have achieved regulatory success. Notably, allogeneic gene therapies remain rare, likely due to challenges in immune compatibility, manufacturing complexity, and safety control.

Interestingly, the US exhibits a pronounced tilt toward allogeneic cell therapies, including numerous HPC and cord blood products, reflecting a regulatory openness to minimally manipulated cell-based interventions. In contrast, Japan has concentrated more approvals on autologous cell-based products (e.g., epithelial cell sheets, cultured chondrocytes), which align with its hospital-centered regenerative medicine model and device-like treatment architecture.

Overall, the comparison illustrates divergent national strategies toward regulating and funding CGTs, shaped by institutional infrastructures, healthcare financing systems, and technological readiness.

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Table 4-24

Number of Approved Cell and Gene Therapies in Different Categories Among the United States, European Union, and Japan (2009-2024)

Type			US	EU		Japan	
			A	**A**	**R**	**A**	**R**
Gene Therapy	*ex vivo*	autologous	12	11	11	5	4
		allogeneic	2	1	1	1	0
	in vivo		10	8	7	4	3
Cell Therapy		autologous	4	5	2	7	1
		allogeneic	16	2	2	3	1
		Total	**44**	**27**	**23**	**20**	**9**

Note. Compiled by the researcher. US = the United States; EU = the European Union. **A** represents Approval; **R** represents Reimbursed.

As for the price among the three systems, the US tends to have higher list prices compared to the EU or Japan. This pricing disparity stems from fundamental differences in the structure of health systems, market dynamics, and regulatory philosophies.

Unlike many countries, the United States lacks a centralized mechanism for negotiating drug prices. Pharmaceutical manufacturers are allowed to set launch prices freely without limitations, although discounts are often negotiated through private insurers; these negotiations lack transparency and rarely impose binding upper limits (Aitken et al., 2020; Kang et al., 2020). In contrast, countries such as Germany, France, the UK, and Japan employ government-led HTA to evaluate clinical benefit, cost-effectiveness, and budget impact before granting market access and reimbursement. For example, the UK National Institute for Health and Care Excellence (NICE), as the HTA body, conducts economic evaluations to determine the cost-effectiveness of new drugs compared with existing alternatives and calculates their incremental cost-effectiveness ratio (ICER). The cost-effectiveness threshold used by NICE is usually between £20,000

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and £30,000 (approximately $37,000) per quality-adjusted life year (QALY), and may be higher for drugs for terminal illnesses or rare diseases (Burki, 2019; Kang et al., 2020).

Interestingly, research by Aitken et al. (2024) has found that CAR-T therapies may have a lower cost compared to other gene therapies, with an average price across geographies of around $350,000, and the prices in the US were higher than those in the EU or Japan.

4.2.3 The Mapping of Technologies and Regulatory Systems of CGTs

Another perspective for evaluating the maturation condition of technologies is the successful examples of commercialization. **Table 4-25** presents a comparative analysis of regulatory approvals of the selected CGTs across the US, the EU, and Japan, revealing distinct strategic orientations in the governance of CGT modalities.

The US leads in both the number and diversity of approved products, particularly in AAV and CAR-T. High-profile examples such as Luxturna, Zolgensma, Hemgenix, Kymriah, and Yescarta underscore the FDA's proactive stance, supported by expedited review pathways like Orphan, RMAT, and Breakthrough Therapy designation. In contrast, the EU exhibits a more cautious and selective approach. While two CAR-T products have obtained conditional marketing authorization through the EMA, several gene therapies, such as Glybera, were initially approved but later withdrawn due to commercial infeasibility or insufficient cost-effectiveness, highlighting the influence of HTA and real-world evidence requirements (Warner, 2017). Japan, meanwhile, demonstrates a distinct pattern. It has approved a notable number of MSC-based therapies, including Stemirac, Temcell, and Akaung, reflecting a system that facilitates earlier market entry for regenerative modalities under post-market surveillance conditions. The differing emphases, the US on accelerated innovation, the EU on clinical and economic

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sustainability, and Japan on structured conditional access, collectively illustrate the global heterogeneity in CGT regulatory ecosystems.

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Table 4-25

The Approval Status of Selected Cell and Gene Therapies in the United States, European Union, and Japan

Modality	Product	US	EU	Japan
AAV	Beqvez	✓	✕	
	Elevidys			
	Glybera		✕	
	Hemgenix	✓	✓	
	Kebilidi	✓		
	Luxturna	✓	✓	✓
	Roctavian	✓	✓	
	Upstaza		✓	
	Zolgensma	✓	✓	✓
CAR-T	Abecma	✓	✓	✓
	Aucatzyl	✓		
	Breyanzi	✓	✓	✓
	Carvykti	✓	✓	✓
	Kymriah	✓	✓	✓
	Tecartus	✓	✓	
	Yescarta	✓	✓	✓
CRISPR	Casgevy	✓	✓	
MSC	Ryoncil	✓		
	Stemirac			✓
	Temcell			✓
MSC Gene Transfection	Akuugo			✓

Note. Compiled by the researcher. US = the United States; EU = the European Union; AAV = adeno-associated virus; CAR-T = chimeric antigen receptor T-cell; CRISPR = clustered regularly interspaced short palindromic repeats; MSC = mesenchymal stem cell; NK Cell = natural killer cell; iPSC = induced pluripotent stem cell.

✓ means approved; ✕ means approved but later withdrawn.

While the strategic grouping of CGT modalities based on patent trajectory and clinical maturity offers a sound theoretical framework, comparing it with real-world

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product approvals reveals key divergences. Notably, CAR-T therapies exhibit a strong alignment between theory and practice, as they are classified as both technologically and clinically mature (Group B) and have received the highest number of regulatory approvals across the US, EU, and Japan. This validates the model's predictive power for well-integrated modalities with consolidated industry backing.

In contrast, MSC falls into Group A, reflecting a pattern of fragmented or stagnant patent development despite an abundance of clinical trials. The approval data support this discrepancy, as MSC therapies are predominantly approved in Japan and less so in the US and EU. This suggests that clinical proliferation in certain jurisdictions does not always correlate with robust intellectual property structures or global market translation.

Meanwhile, technologies in Group C, including AAV, CRISPR, iPSC, and NK cell therapies, exhibit a mixed picture. Although they are theoretically positioned as emerging or transitional, several have already achieved regulatory approvals. For instance, AAV-based therapies (e.g., Elevidys and Glybera) and CRISPR-based therapies (e.g., Casgevy) have received market authorization. This suggests that platform-based modalities may advance clinically through specific, high-impact applications, even if the broader innovation landscape remains fragmented or immature.

However, compared to CRISPR, AAVs, which are the technology with the largest number of approved products, tell a different story. First of all, AAVs are found that almost every one of them targets rare diseases. For example, Beqvez and Hemgenix target Hemophilia B, which occurs in newborns with a possibility of 0.02% in the US (National Bleeding Disorders Foundation, n.d.); Luxturna targets retinitis pigmentosa, which occurs in about one out of every 4,000 people worldwide (Lim et al., 2020); Zolgensma targets spinal muscular atrophy (SMA), for which the estimated occurrence of SMA is 1 per 10,000 live births worldwide (Sarv et al., 2021).

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Secondly, AAV has been the most frequently targeted asset in several merger and acquisition (M&A) deals. Among the ten gene therapy M&A deals that occurred during 2018 and 2019, 80% involved companies holding AAV-related technology or products (Vandermosten, 2020). This indicates that the industry is optimistic toward the commercial potential of AAV. Nonetheless, several M&A activities have ripened into successfully marketed products, such as Zolgensma, which originated from AveXis, acquired by Novartis in 2018, and Luxturna, which was brought to Roche through the acquisition of Spark (Keown, 2019).

However, it is observed that the large pharmaceutical companies have been pulling back their exploration of AAV (Smith, 2025), which is also reflected in the smaller number of clinical trials of AAVs. Many factors contribute to the result. One of the challenges is the small patient population, which has made generating profits from AAV products difficult, and no viable business model has been established. Also, the increasing regulatory evaluation criteria, small payload size, and the mismatch between the cost and outcome have dissuaded the industry from further engaging in the technology (Peter, 2025; Smith, 2025).

Regarding the reimbursement criteria, the country's influence is greater than the modality itself. For example, the EU reimburses almost every CGT listed in **Table 4-25**.

Overall, this comparison demonstrates that regulatory approval is not always a direct indicator of technological maturity. External factors, such as disease urgency, regulatory incentives (e.g., orphan drug status), and targeted innovation strategies, can facilitate early market access, particularly for platform technologies.

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4.3 CGTs in Taiwan

4.3.1 The Regulatory Evolution of CGT

The Regulation Governing the Application of Specific Medical Examination Technique and Medical Device in 2018

Taiwan's CGT development has undergone a significant shift over the past decade. In 2016, the Ministry of Health and Welfare (MOHW) restructured Taiwan's regulatory framework for overseeing CGTs, encompassing both medical practices and medicinal products. Under this framework, certain autologous cell therapies, which are designated for specific indications, have been regulated as medical practices rather than drugs. These therapies fall under the jurisdiction of the Department of Medical Affairs (DOMA) and have been governed since September 2018 by the Regulation Governing the Application of Specific Medical Examination Technique and Medical Device (RASMET). Given the availability of substantial international safety and efficacy data, these autologous therapies are classified as low-risk interventions. In February 2021, the DOMA updated RASMET to broaden its scope to cover allogeneic cell therapies with enough clinical evidence. Medical institutions planning to administer these therapies must submit detailed treatment plans for approval (Chao et al., 2023).

This had resulted in a "dual-track regulatory pathway" in Taiwan. Cell therapies are further divided into medical practices and standardized products. The RASMET was regulated by the practices under DOMA, while commercialized products still required market authorization from the Taiwan Food and Drug Administration (TFDA) (Chao et al., 2023).

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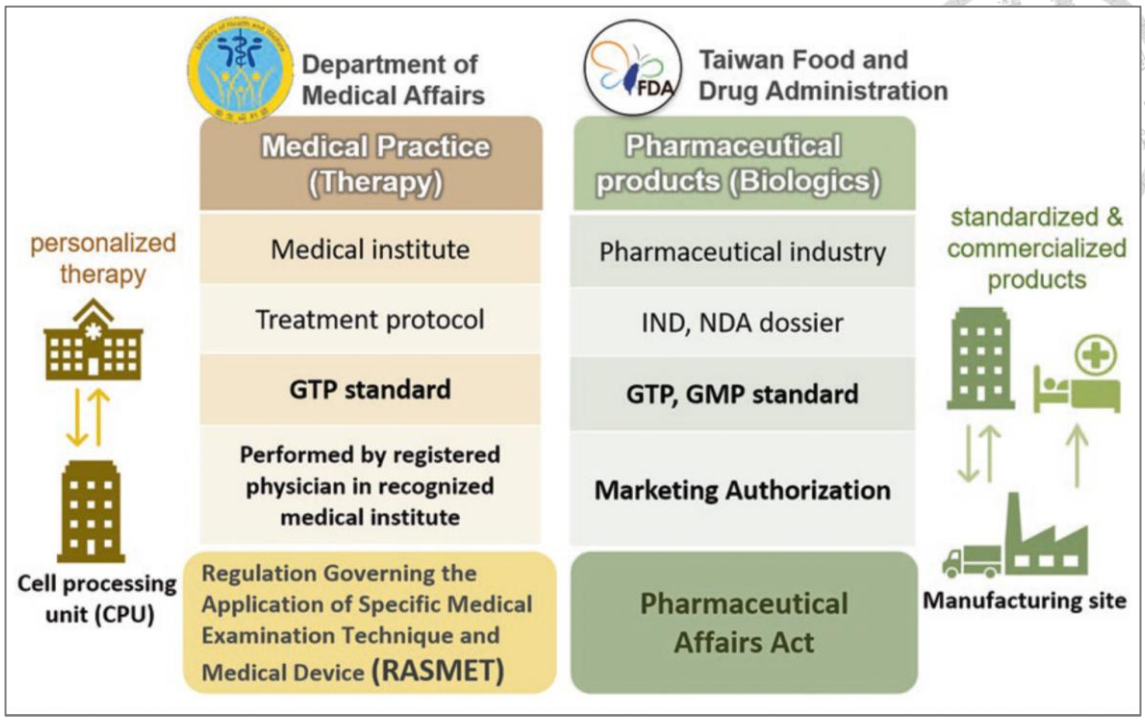

Figure 4-28

Dual-Track Regulatory Pathway in Taiwan

Note. Reprinted with permission from "Update on Regulation of Regenerative Medicine in Taiwan" by Wan-Yu Chao, Yi-Ting Chang, Yueh-Tung Tsai et al, 2023, "In Regulatory Aspects of Gene Therapy and Cell Therapy Products: A Global Perspective", pp. 211-219 (https://doi.org/10.1007/978-3-031-34567-8_12). Copyright 2023 by Springer, Cham.

The "Dual-Regenerative Acts" in 2024

On June 4, 2024, a significant legislative milestone was achieved as the Legislative Yuan approved both the Regenerative Medicine Act (RMA) and the Regenerative Medicinal Products Act (RMPA) (DOMA, 2024a, 2024b), often is referred to as the "Dual-Regenerative Acts", which designed to fill critical gaps in current medical practice, especially for patients with severe or life-threatening conditions lacking effective treatment options (O. Wu, 2025). CGT is therefore more thoroughly included in the regulatory system. The terms in this Act are defined as follows:

1. Regenerative medicine: Products or techniques that utilize genes, cells, and their

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derivatives for the treatment, repair, or replacement of human cells, tissues, and organs.

2. Regenerative medicinal products (hereinafter referred to as "regenerative products"): Products containing genes, cells, and their derivatives intended for human use.
3. Regenerative medicine techniques (hereinafter referred to as "regenerative techniques"): Regenerative medicine techniques performed on the human body (MOHW, 2024).

Legal and Ethical Controversies

The legislative process of the "Dual-Regenerative Acts" has generated significant academic and public debate, primarily focusing on the balance between regulatory flexibility and patient safety. Key controversies are outlined below.

1. Permissive Conditions under Article 9 and Associated Risks

   A major point of contention lies in Article 9, Paragraph 1, Subparagraphs 2 and 3 of the RMA draft. These clauses permit the clinical application of allogeneic cell therapies in non-emergency contexts based solely on preliminary human trial data or existing evidence from domestic or international studies. Notably, the law does not restrict such interventions to life-threatening or severely debilitating conditions (Yang & Lin, 2023; You, 2024).

   Academics and patient advocacy groups have criticized this regulatory leniency for creating a legal loophole that allows unproven regenerative technologies to enter clinical use prematurely. Concerns center around the potential for patient harm due to insufficient efficacy and safety data, as well as the economic burden imposed by expensive therapies that may offer limited or no clinical

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benefit. Such conditions may also increase the risk of misinformation and exploitation, particularly among vulnerable patient groups (editorv, 2024b; Liu, 2025).

The clause was later amended to require that all regenerative procedures and products pass Phase II trials before being applied to patients in the official RMA (You, 2024).

2. Informed Consent and Patient Protection

Given the complexity of regenerative therapies and the asymmetry of information between providers and patients, civil society organizations have expressed concerns regarding the adequacy of informed consent mechanisms. There is a risk that patients and their families may be subjected to aggressive marketing of high-cost interventions whose therapeutic value remains uncertain. To safeguard patient autonomy and the right to health, critics argue for more stringent oversight, enhanced transparency of information, and institutional accountability (editorv, 2024a; Yang & Lin, 2023).

A website named “Cell therapy technology information zone,” provided by MOHW, was launched in 2010 to enhance the transparency of the CGT information to the patients, where they can search for qualified and approved medical facilities for different treatments (DOMA, 2010).

3. Industrial Promotion vs. Ethical Risk

Proponents of the legislation emphasize its potential to spur innovation, attract investment, and curb the proliferation of unregulated underground practices (Huang, 2024; Lai & Jiang, 2024; P. A. Wu, 2025). However, opponents warn that excessive deregulation may accelerate the commercialization of healthcare, consolidate power among interest groups, and expose socially disadvantaged

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populations (editorv, 2024a; Liu, 2025). These concerns underscore the ethical dilemmas inherent in promoting industrial development while prioritizing public health.

4. Vacancy of Subsidiary Regulations

   Following the enactment of the primary legislation, MOHW has begun releasing supplementary regulations governing various aspects of regenerative therapy administration. These include technical assessment protocols, clinical trial requirements, institutional accreditation, public disclosure obligations, and adverse event reporting mechanisms (P. A. Wu, 2025). However, there is still much to be done, as the industries remain uncertain about the regulatory constraints and will not be able to respond in time (Interviewee A, 2025).

The official version of RMA has amended several controversial articles in the draft that were widely criticized, including:

- The definition of “regenerative medicine” does not exclude the use of allogeneic or xenogeneic cells and tissues. However, in the case of compassionate use, an exceptional pathway that allows treatment without completing clinical trials, the use of xenogeneic cells or tissues is explicitly prohibited.
- The exemption from conducting clinical trials has been revised to apply only under two specific circumstances: first, in the case of compassionate use; and second, for regenerative technologies that were approved under the RASMET prior to the implementation of the RMA, which may continue to be used without completing domestic clinical trials.
- The controversial provision allowing hospitals to establish regenerative medicine-related biotech or pharmaceutical companies has been removed.

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- Fetal tissue is prohibited from being used as a source of cells, and consent from individuals with no or limited legal capacity must be notarized to be considered valid.
- Research involving ethically contentious practices, such as the creation of chimeras through artificial fertilization or the propagation of embryos for research purposes, is strictly prohibited.
- MOHW is required to publicly release an annual report, which must include not only the number of cases, treatment outcomes, and adverse events, but also expanded details covering key indicators of medical quality, such as the number of approved medical institutions, total number of enrolled patients (including those who completed the full course of treatment and those who did not), reported adverse events, and clinical evaluation metrics (Huang, 2024).

Despite ongoing discussions surrounding Taiwan's dual-track regenerative medicine legislation, the regulatory department's efforts to advance the regenerative medicine industry are recognized by CGT companies. However, the department should shift its mindset from overseeing the industry to coaching it, similar to the US FDA (Interviewee D, 2025).

Nonetheless, the controversies still underscore a broader tension between innovation-driven policy frameworks and the ethical imperative to protect patient welfare. Central to the controversy is the question of whether unproven therapeutic modalities should be permitted in non-critical scenarios, and how legal systems can prevent regulatory capture while ensuring equitable, transparent, and safe access to emerging biomedical technologies.

The constantly changing regulations and unstable political environment are resulting

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in a trust issue between industries and the government. Since they cannot be sure when the cell therapies regulations will be changed again, capable companies tend to prepare for both scenarios, namely, providing therapies and applying for drug authorization simultaneously. At the same time, the clinical data they gather in Taiwan may be leveraged in other Asian countries due to shared racial backgrounds (Interviewee A, 2025).

4.3.2 The Development of CGTs

In the regenerative medicine industry, upstream companies primarily focus on collecting and preserving various stem cells and tissues, including operating cell banks. Midstream enterprises are engaged in the development of functional products derived from immune and stem cells. Downstream firms are responsible for conducting clinical trials, advancing transplantation technologies, and delivering therapeutic applications for disease treatment (*Chǎn yè jià zhí liàn zī xùn píng tái [Industrial Value Chain Information Platform]*, n.d.). The current landscape of the Taiwanese companies in the industrial chain is illustrated in **Figure 4-29**.

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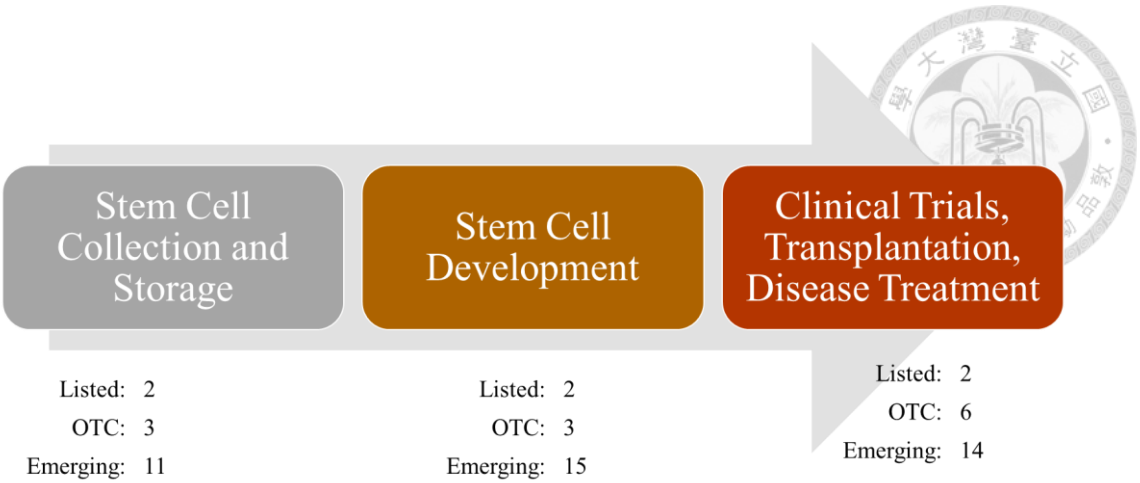

Figure 4-29

The Industrial Value Chain of Regenerative Medicine in Taiwan

Note. Adapted from *Chǎn yè jià zhí liàn zī xùn píng tái [Industrial Value Chain Information Platform]* (n.d.). The numbers below present the Taiwanese companies in the regenerative medicine sector listed on the stock market. Some companies may appear more than once. Listed = listed stock; OTC = over-the-counter stock; Emerging =. Emerging stock board.

The supply chain of a successfully delivered CGT also requires the transportation of cellular products or semi-products. The cold chain logistics in Taiwan have developed into quite efficient systems; it takes only four hours to deliver the product from Taipei to Pingdong, which is approximately 370 kilometers away. However, quality control and monitoring during transportation can be improved to enhance global recognition (Interviewee D, 2025).

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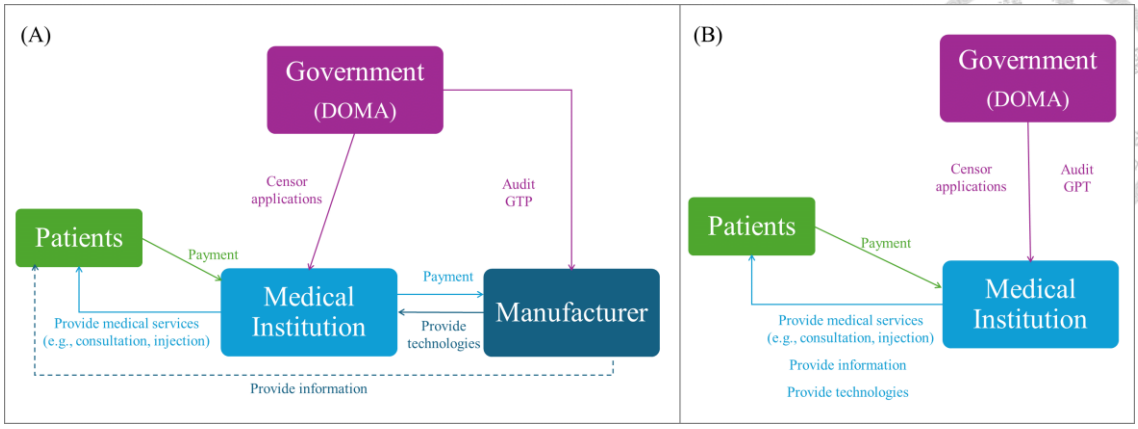

Figure 4-30

Interaction Frameworks Among Stakeholders in Taiwan's Cell and Gene Therapy Ecosystem

Note. Compiled by the researcher from Interviewee B, 2025. DOMA = Department of Medicine Affairs.

Figure 4-30 illustrates the two current operational structures of CGT being provided to patients under the framework of RASMET or RMA. The main difference between the two is the qualification of the medical institution, whether it incorporates a cell preparation facility within the institution. Since CGT is regarded as a medical procedure, it can only be performed in a medical institution; thus, the only point of contact between the patient and the therapy is the medical institution. Meanwhile, the government should examine the entire process to ensure the final CGT presented is safe and qualified.

CGT as Procedures

Since November 2018, the Taiwan Center for Drug Evaluation (CDA) has been accepting applications for the cell therapy program. By the end of 2022, a total of 399 cases had been filed, and the number increased to 502 by the end of 2023. The modalities of approved cell therapy programs are displayed in **Figure 4-31**, with autologous immune

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cells being the most utilized, accounting for 60%. Among the immune cells that have been selected, cytokine-induced killer cells (CIKs) are the most prominent.

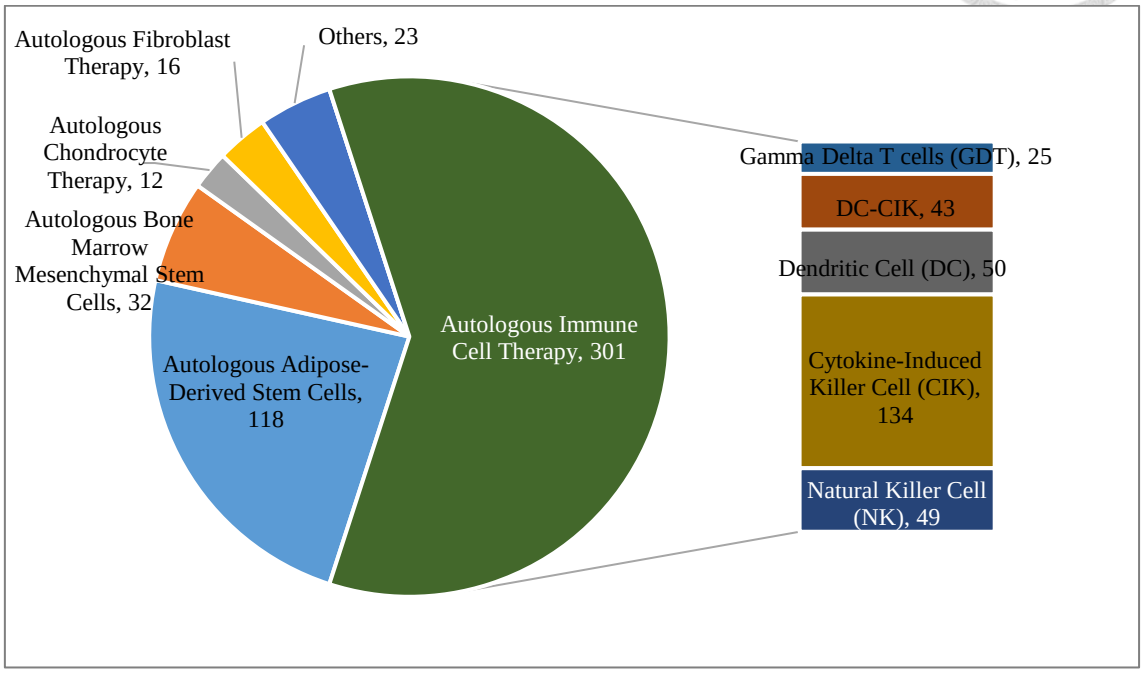

Figure 4-31

Number of Applications by Cell Therapy Technology (as of December 31, 2023)

Note. Compiled by the researcher, data from the 2024 Annual Report of Cell Therapy (MOHW, 2025a).

As for the indications that have been filed, shown in **Figure 4-32**, most are solid tumors, followed by degenerative arthritis and knee cartilage defects.

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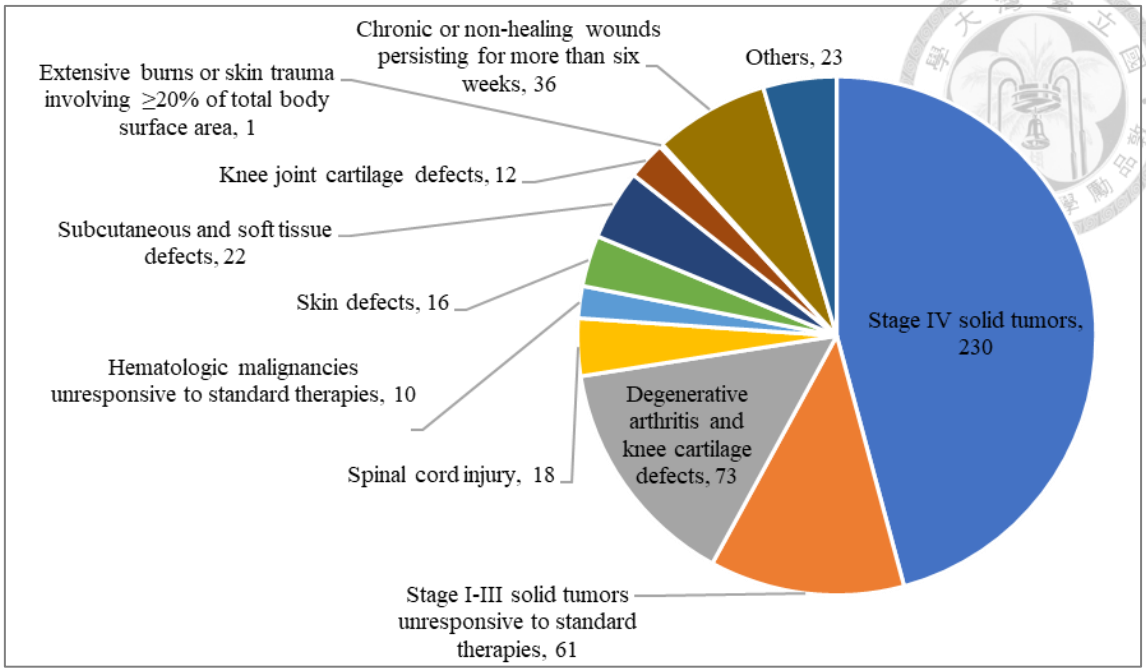

Figure 4-32

Number of Applications by Cell Therapy Indications (as of December 31, 2023)

Note. Compiled by the researcher, data from the 2024 Annual Report of Cell Therapy (MOHW, 2025a).

As of December 31, 2023, a total of 305 applications were granted, and 47 were suspended; therefore, the net number of authorized cell therapy treatments is 258 cases. These cell therapy treatments are executed by 77 medical facilities, most of which are regional hospitals. The total number of patients receiving the treatments is 1,201; 732 of them have completed the treatment (MOHW, 2025a).

CGT as Drugs

As of October 2024, the TFDA had approved six regenerative medicine products for market entry, all of which are imported: Zolgensma (by Novartis), Kymriah (by Novartis), Luxturna (by Spark Therapeutics), Novartis' Luxturna, Roctavian (by BioMarin), and Upstaza (by MassBiologics). In terms of ongoing development, there were 153 active

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clinical trials for regenerative medicinal products ongoing in Taiwan, including 102 trials focused on cell therapies and 51 on gene therapies (Liu, 2024).

While the increase in clinical trials reflects a growing institutional interest and regulatory flexibility in regenerative medicine, it is worth noting that clinical activity alone is not sufficient to ensure broader access to CGTs. Without addressing post-commercialization challenges, such as high treatment costs, manufacturing and delivery infrastructure, and, most critically, the development of sustainable reimbursement systems, the benefits of these therapies may remain inaccessible to most patients. Therefore, expanding trial capacity must go hand in hand with strengthening Taiwan's readiness for the commercial adoption of CGT.

4.3.3 The Payment and The Reimbursement State of Taiwan's CGT

National Health Insurance

Under the dual-track system of Taiwan, CGTs are further categorized by therapies and market-authorized drugs. Currently, not all therapies are reimbursed, and patients must self-fund their care. In contrast, certain approved drugs can be reimbursed by Taiwan's National Health Insurance (NHI).

Taiwan's National Health Insurance was launched on March 1, 1995, and is regulated by the National Health Insurance Administration (NHIA) (NHIA, n.d.-b). It is a compulsory program and covers almost the entire population in Taiwan. The benefit package is extensive, including inpatient and outpatient care, dental services, traditional Chinese medicine, and prescription medications (NHIA, 2024).

According to Article 4 in "National Health Insurance Drug Benefit Items and Payment Standards": "…For drug benefit items not included in this standard, insurance medical service institutions or drug dealers or medical equipment manufacturers that meet

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the following conditions may propose to the insurer to set a list of items to be included…"(MOHW, 2025b). The pharmaceutical companies or their local distributors can therefore propose to the MOHW that their product be included in NHI coverage. According to the 2023 statistical data, the expenditure on national health insurance was NT$782,421 million, accounting for 42.65% of the total national health expenditure (Department of Statistics, n.d.). Thus, the inclusion of medical products into NHI coverage, especially for CGTs, is more strategically important due to their high prices.

Among the four TFDA-approved CGTs in Taiwan, only two were further included in NHI coverage, as shown in **Table 4-26**. Both of which underwent price adjustments and adopted outcome-based or temporary reimbursement mechanisms.

Table 4-26

The Cell and Gene Therapies included in Taiwan's National Health Insurance

Drug Name	Reimbursement Price (NTD)	Company	Approved Date
ZOLGENSMA Suspension for Intravenous Infusion	49,000,000	Novartis Taiwan	August 1, 2023
KYMRIAH suspension for intravenous infusion	8,198,096	Novartis Taiwan	November 1, 2023

Note. Compiled by the researcher from the National Health Insurance Administration (NHIA), accessed on May 30, 2025.

The inclusion of Zolgensma was first discussed on June 15, 2023. The reimbursement price was initially set at NT$59,216,645 per dose, based on the international median price. However, since the company recommended NT$49,000,000 per dose, the lower price was adopted (NHIA, 2023a). Nonetheless, the reimbursement payment will be based on efficacy. Thus, the financial impact was evaluated as none.

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Additionally, patients receiving the treatment are required to attend follow-up visits to monitor the treatment's efficacy. If the term is not followed, NIH will not cover the subsequent treatment (NHIA, 2023b).

A similar story happened with the inclusion of Kymriah as well. The reimbursement price was first set at NT$1,107,332 per dose, based on the international median price of 10 countries. However, the company recommended NT$8,198,096 per dose, but the lower price was adopted. Meanwhile, the costs of cell separation and preservation incurred during the treatment period should also be covered by the drug (NHIA, 2023b). Additionally, the inclusion of Kymriah was under a “Temporary payment” pathway, while providing patients with health insurance resources. NHIA also collects real-world data to assess whether to continue providing health insurance benefits that cover Kymriah in the future (Lin, 2023).

Outcome-based Payment under RASMET

On the other hand, concerns arose soon after RAMSMET was launched regarding self-sponsored payments for therapies, as high charges were levied without a guarantee. Thus, MOHW has specifically addressed the issue, stating that hospitals implementing cell therapies are required to adopt a staged payment model based on treatment outcomes and must submit proposed payment or refund arrangements for various scenarios to the local health authority for approval. The scenarios include failure to produce cell products meeting specifications (due to insufficient sample quantity), patients being physically unfit to continue the treatment, and the treatment course being unable to be completed as planned due to other unforeseen circumstances (MOHW, 2019). For example, a three-stage payment collection has been established in China Medical University Hospital (CMUH) and Hualien Tzu Chi Hospital. After a thorough evaluation, the patient and

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hospital agree to proceed with cell therapy. At this stage, the hospital charges an initial 5% fee and begins cell preparation. During treatment, fees are charged per dose administered. The final 10% payment is collected only if the therapy meets the outcome criteria approved by the MOHW (Liu, 2020).

The payment schemes for medical facilities offering cell therapies were established during the RASMET period. For example, a DC-CIK treatment for Phase IV solid cancer provided by CMUH is charged in 3 stages: the first two stages cover cell preparation, and the remaining stages are charged by doses. Finally, an evaluation will be conducted to determine if the outcome meets the indicators, allowing for the collection of the final payment (MOHW, n.d.).

Commercial Insurance

Commercial insurance in Taiwan is gradually evolving to address the financial burden posed by the high costs of regenerative medicine. While traditional reimbursement-based plans typically offer coverage up to NT$500,000–550,000, this remains inadequate given the million-dollar scale of some advanced therapies. In response, lump-sum products, such as critical illness and cancer insurance, provide more flexible financial support, offering substantial payouts upon diagnosis that can be applied to a wide range of treatment options, regardless of the modality (Interviewee C, 2025; We Get Care, 2025).

Some insurers have also begun to introduce treatment-specific or multi-payout policies, which may accommodate newer therapeutic approaches. For instance, Nan Shan Life introduced Taiwan's first commercial coverage for autologous immune cell therapy for stage IV solid tumors in 2020 through an add-on rider (Liu & Hung, 2024).

Currently, receiving cell therapy does not require hospitalization. Patients typically

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spend only a few hours on procedures such as blood collection for cell preparation or return for injections or infusions once the cells are ready. However, some patients request to stay in the hospital for a day to claim additional insurance benefits (Interviewee B, 2025).

For medical institutions that provide CGT procedures, product liability insurance serves as a possible remedy for unhappy situations. However, it is difficult for patients to prove the relationship between the injury and the cell therapy, or that the hospital was negligent in performing the cell therapy. (Chen, 2023).

Nevertheless, CGTs are still largely not covered by standard commercial insurance worldwide due to their high costs and limited long-term data. Whether broader inclusion will occur depends on accumulating sufficient clinical and economic evidence to support risk pooling and actuarial viability.

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Chapter 5 Conclusion

5.1 Study Findings

5.1.1 The Establishment of a Systematic Structure for CGT Analysis

This study developed a systematic analytical framework for CGT by integrating multiple dimensions, including technology development, clinical maturity, and patent dynamics. The inclusion of AI has further facilitated the analysis, making it more efficient and more comprehensive.

Based on the collected data, a strategic grouping (see **Figure 4-26**) was established to categorize the six selected CGT modalities.

- Group A, represented by MSC, consists of modalities with relatively fragmented or stagnant technological development. Despite limited innovation, these therapies have achieved wide clinical acceptance, as evidenced by a substantial number of clinical trials.
- Group B, exemplified by CAR-T, exhibits a more balanced profile, characterized by a well-defined patent trajectory and extensive clinical engagement. The convergence of innovation and adoption suggests the emergence of a “dominant design” with the potential to become industry standards. Increasing participation from large pharmaceutical companies may indicate growing market confidence.
- Group C, including AAV, NK cell, CRISPR, and iPSC, represents modalities that are still immature in at least one dimension. Some, such as CRISPR and NK cell therapy, are technologically emerging, while others, like iPSC, remain at an exploratory stage in terms of clinical application.

Figure 5-1 provides a visual presentation of the developmental status of CGTs across

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three dimensions: technological development, clinical application, and applicant landscape. Modalities in Group C exhibit relative weakness in one or more of these dimensions. Particularly, NK cells appear to be evenly developed across all three aspects, which are considered the next rapidly advancing modality based on the results of the strategic grouping following CAR-T.

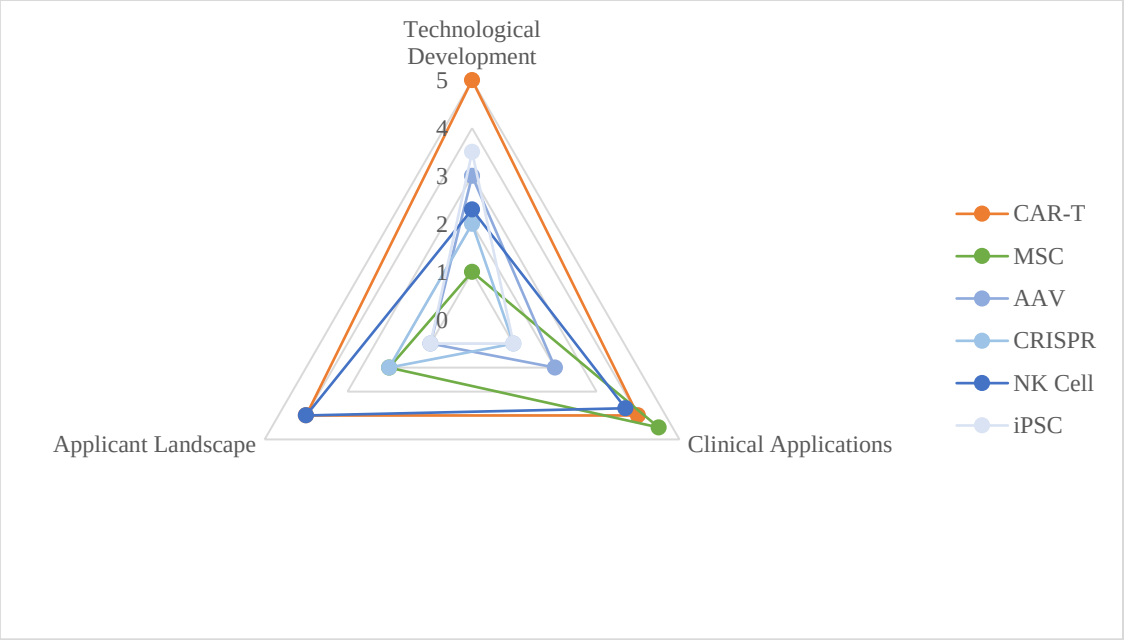

Figure 5-1

Comparison of Cell and Gene Therapy (CGT) Modalities Based on Technological Development, Clinical Applications, and Applicant Landscape (1976-2024)

Note. Compiled by the researcher. The scores for applicant landscape and clinical applications represent relative comparison values across the selected CGT modalities.

However, inconsistencies are observed when comparing the grouping results to the actual approval landscape. In particular, AAV and CRISPR have achieved market approvals despite not appearing to be the most mature in terms of technological convergence or clinical adoption. This implies that successful commercialization depends not only on scientific and clinical development but also on regulatory incentives and

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alignment with market needs. Notably, although AAV is regarded as the frontier of gene therapies according to the literature, the deceleration of AAV-related innovations and the limited number of ongoing clinical trials, yet a large number of approved products and M&A activities suggest that this modality may be entering the saturation phase of the technology life cycle, unless a viable business model is developed to fuel the market interest.

An additional finding emerged from the patent citation network analysis: several patents appeared across multiple CGT modalities (see **Table 5-1**). This overlap may reflect the presence of core platform technologies, such as engineered immune receptors and genome editing systems, that serve as foundational components in both gene and cell therapies. Moreover, the recurrence of these patents may indicate strategic patent positioning by influential institutions seeking to expand their presence across multiple therapeutic domains. The pattern also suggests that the boundaries between CGT modalities remain fluid, with convergence trends yet to stabilize within a clearly defined industrial structure.

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Table 5-1

Repeated Patents Found in the Six Cell and Gene Therapies' Patent Citation Network (1976-2024)

Patent No.	Topic	Applicant	Modalities that include the patent
US11866726B2	Systems and methods for targeted integration and genome editing and detection thereof using integrated priming sites	Editas Medicine, Inc. (US)	CRISPR, MSC, iPSC, AAV
US11661459B2	Artificial cell death polypeptide for chimeric antigen receptor and uses thereof	Century Therapeutics, Inc. (US)	AAV, NK cell, iPSC
US10869898B2	Methods and compositions for immunomodulation	Rubius Therapeutics, Inc. (US)	MSC, iPSC
US10105436B2	Smallpox vaccine for cancer treatment	Calidi Biotherapeutics, Inc. (US)	MSC, iPSC
US12104178B2	DHFR tunable protein regulation	Obsidian Therapeutics, Inc. (US)	CAR-T, NK cell
US11680941B2	Assays for potency of human retinal pigment epithelium (RPE) cells and photoreceptor progenitors	Astellas Institute for Regenerative Medicine (US)	MSC, iPSC
US11422125B2	Assays for potency of human retinal pigment epithelium (RPE) cells and photoreceptor progenitors	Astellas Institute for Regenerative Medicine (US)	MSC, iPSC
US12060576B2	Compositions and methods for producing megakaryocytes	Stellular Bio, Inc. (US)	MSC, iPSC
US11674121B2	Platform for generating safe cell therapeutics	The Regents of the University of California (US)	MSC, iPSC
US12049644B2	Platform for generating safe cell therapeutics	The Regents of the University of California (US)	MSC, iPSC
US11248213B2	Platform for generating safe cell therapeutics	The Regents of the University of California (US)	MSC, iPSC
US12037407B2	Immune cells having co-expressed shRNAS and logic gate systems	Arsenal Biosciences, Inc. (US)	AAV, CAR-T

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Finally, the six CGT modalities selected in this study are all autologous platforms.

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While this approach has facilitated early-stage translation and clinical adoption, its scalability and cost-effectiveness remain limited. Given that some of these autologous-based modalities, such as MSC and CAR-T, are entering the maturity phase of the technology life cycle, manufacturers should begin exploring a “second S-curve” for growth. This may involve transitioning toward allogeneic platforms, integrating gene-editing tools, or leveraging modular manufacturing systems to improve scalability and reduce unit cost. Strategic foresight in this direction will be essential for sustaining competitiveness as the field moves beyond the initial wave of innovation.

5.1.2 The Heterogeneous Global Environment of CGT

Although the need to revise HTA criteria for CGT has been widely acknowledged, a harmonized transition has yet to occur. This lack of standardization increases the complexity of bringing CGT products to international markets. Pricing uncertainty and variability in market acceptance remain key challenges for developers. The design of payment systems varies across different systems, making it difficult to adopt a single model.

The regulation of CGT has evolved into two distinct mindsets: CGT is regulated either as a procedure or as a drug. The US and EU manage CGT applications only in the drug examination pathways, which makes it easier to control and unify the standard, but may lead to higher R&D costs and longer clinical validation time. On the contrary, Japan and Taiwan adopt the “Dual-Track Regulatory System,” which provides more flexibility by perceiving CGT as a procedure as well, thereby enhancing clinical accessibility and encouraging innovation. However, the vague definition between the two may result in commercial abuse of the system and compromise patients’ rights. The diversity of the system mindset also leads to developers having different preferences regarding their

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applications; for instance, Taiwan has a higher involvement in CGT procedures than in CGT drugs.

Many countries have adopted innovative payment models that emphasize value-based pricing to manage the high cost of CGTs. However, these mechanisms often rely on bilateral negotiations and are constrained by fragmented payer systems, particularly in regions like the United States and the European Union. In contrast, systems with centralized negotiation authority, such as Japan's NHI and Taiwan's NHI, offer more unified structures but face sustainability concerns due to the budgetary impact of high-cost therapies.

The study also found that the inclusion of reimbursement into either the national system or private insurance is irrelevant to the CGT modality. Still, distinct preferences across regulatory and reimbursement systems are also evident, which is a prerequisite for discussing reimbursement. For instance, the US is relatively open to allogeneic cell therapies, while Japan and the EU are more conservative. In reimbursement terms, the EU shows a higher inclusion rate of CGTs in public insurance systems, whereas Japan adopts a cautious, conditional approval approach with tighter post-marketing requirements.

To sum up, when discussing the inclusion of payments or the method of CGTs, the market authorization pathways should be the priority for consideration, followed by the HTA criteria, as they relate to the final decision on the price.

5.1.3 A New Strategic Pillar in Biotechnology for Taiwan

Compared to molecular medicine or biological drugs, CGT has not yet been dominated by large pharmaceutical enterprises, which provides a vast opportunity and stage for Taiwanese biotechnology companies to explore.

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From the initial implementation of RASMET in 2018 to the recent enactment of the Dual-Regenerative Acts in 2024, Taiwan has progressively developed a dual-track system that distinguishes between medical practice and commercialized products. While these reforms have accelerated CGT access and fostered industry development, they have also raised critical legal and ethical concerns, particularly regarding regulatory consistency, evidence thresholds, informed consent, and commercialization risks. The controversies underscore the necessity for robust subsidiary regulations, transparent oversight, and ethical safeguards to ensure that patient welfare remains central in policy design.

The payment system of CGTs in Taiwan has not yet been integrated into a comprehensive system. Both NHI and commercial insurance in Taiwan are still in the early stages of incorporating CGTs into their coverages. NHI, being the primary payer in Taiwan's healthcare system, will prioritize sustainability when designing the system, and the inclusion of commercial insurance is crucial. An innovative payment scheme is already being implemented in real-world practices, e.g., the outcome-based payment under RASMET. However, this payment method protects patients but may incur significant additional costs for developers. The mitigation between the two stances, and building an integrated CGT payment system to support treatment accessibility relies on the government to lead, and the joint contribution of the industries.

5.2 Strategy Suggestions

5.2.1 Different CGT Modality and Payment System

1. Industrialization as a Prerequisite for Payment System Design

Before discussing payment systems, the potential for industrialization must be evaluated. From an industry development perspective, technologies that serve multiple, highly customized applications, such as AAV and MSC, face difficulties in

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standardization and scaling. These modalities are tailored to specific clinical needs rather than built upon a defined technological trajectory, making mass production and institutional integration challenging. For example, considering the large number of approved AAV products, the limited number of ongoing AAV trials may indicate that its clinical potential is approaching saturation. Therefore, the future of AAV development depends on the development of new applications and progress in clinical research. As these technologies have yet to establish industrial standards, it is premature to design dedicated payment systems for them.

In contrast, CAR-T therapies exhibit characteristics that align with industrial scalability. In biomedicine, the commercialization of a therapy typically requires a tight link between a specific indication and a reproducible manufacturing process. CAR-T has developed along a clear technological trajectory, primarily in oncology, and its therapeutic effect has been validated through multiple approvals. The increasing involvement of large pharmaceutical firms reflects confidence in their economic potential, as major investors generally avoid high-risk or non-scalable ventures. As such, CAR-T is likely to evolve into a core CGT modality, with ongoing efforts focusing on transitioning from autologous to allogeneic platforms to reduce production costs further and expand access.

NK cells appear to be following a similar path. While CRISPR and iPSC remain at an earlier stage of development, NK cells are beginning to exhibit features associated with scalability, including increased activity from major industry players. If future research identifies clear and compelling indications, NK cells could represent the next industrializable CGT modality.

2. Principles for Managing CGT Payment and Institutional Design

From a policy perspective, discussions about the payment system must be grounded

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in the industrial maturity of technology. Without a feasible pathway toward industrialization, payment mechanisms risk becoming fragmented case-by-case exceptions rather than system-level solutions. The core consideration should be whether the technology is likely to be scaled, standardized, and integrated into clinical practice. This includes evaluating whether it complements or replaces existing therapeutic approaches and whether it delivers measurable improvements, such as reduced hospitalization time or lower overall treatment costs.

For mature and application-specific technologies, such as CAR-T, governments should proactively create regulatory and industrial conditions that support commercialization. Due to the high treatment costs associated with CGTs, policymakers should also consider the involvement of commercial insurance to distribute financial risks and build a more resilient payment system.

Conversely, for modalities that have not yet achieved critical mass or exhibit high technological divergence, a more cautious and observational stance is warranted. These technologies may still require time to converge into a dominant design or to reveal a "killer application" that justifies broad institutional support.

In summary, this study finds that among all current CGT modalities, CAR-T is the most suitable candidate for near-term system integration and payment innovation. NK cells also show promise, though their development is less advanced. Other modalities remain in early exploratory phases and require further evidence before policy frameworks can be meaningfully discussed.

5.2.2 Shaping the Future of CGT in Taiwan

Taiwan's CGT industry remains in its early phase of development, with its regulatory and payment systems still transforming. As international practices continue to evolve,

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Taiwan must respond with strategic agility. From the perspective of industry stakeholders, the primary, and arguably most critical, bottleneck lies in the regulatory framework, which ultimately determines whether firms will deepen their engagement in CGT development or shift their investments elsewhere.

1. Choosing the Path

From the comparison of international records of CGT approvals, it is observed that the design of regulatory systems and preferences highly affect the evolving direction of CGTs.

To facilitate Taiwan's CGT industry and break the deadlock, the Taiwanese government must identify promising CGT and encourage the development of the CGT industry chain to enhance the resilience of CGT companies in Taiwan. For example, the current status quo is that Taiwan's CDMO companies are in a relatively passive position, waiting for Clinical Research Organizations (CROs) or pharmaceutical companies to place orders and establish their standards. This phenomenon is widespread in a newly developing field like CGTs. The preparation of a production line for a particular therapy can take years. Unless Taiwan's pharmaceutical manufacturing industry can foresee the future, it will always lag behind other countries.

To better guide the potential future direction of the industry, a tool that helps them precisely choose which modality or technology to engage with and invest in is where the study can make a significant contribution.

This study presents an overview of the current development and landscape of CGTs. The CGT modality that holds the potential for further industrialization and commercialization is identified as CAR-T, and NK cells are seen as a potential next option. However, the presence of large companies in both modalities also suggests that Taiwanese

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CGT companies joining will likely be followers, resulting in lower profits. If the goal is to pursue higher profits, the decision of which CGT will be crucial, since the modalities from Group C are still in an immature stage, waiting for the emergence of a "dominant design" or the revelation of a "killer application". Furthermore, the various expedited pathways must be leveraged to enter the market more quickly; thus, rare diseases will be a promising field to explore.

2. From Governing to Supporting

Currently, the attitude of the regulatory department is still perceived as that of a supervisory unit, rather than a supportive and helpful one. It is suggested that the government should take a more proactive approach in facilitating CGT companies to comply with the standards or work together to find a solution that allows them to fit into the current system, rather than rejecting them once they do not meet the conditions. Certain approaches can be considered, such as:

A. Align Taiwan's regulatory standards with international frameworks, such as those of the FDA, EMA, or PMDA, to improve interoperability and facilitate cross-border commercialization for domestic manufacturers.
B. Recognize the practical barriers to generating large-scale clinical evidence for CGTs and adopt expedited pathways and conditional approvals to support early market entry while ensuring ongoing safety and efficacy monitoring.
C. Refine Taiwan's HTA framework to better account for the long-term, curative potential of CGTs, incorporating elements such as real-world evidence (RWE), quality-of-life impact, and delayed cost-offsets.
D. Establish a fair and transparent mechanism for the use of RWE in regulatory and reimbursement decisions. Under Taiwan's dual-track system, companies

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may generate clinical data through non-commercial channels and subsequently use that data to obtain marketing authorization. While this can accelerate innovation, it may also raise equity concerns, as firms could benefit from both revenue generation and regulatory privileges using the same dataset. To mitigate this, a formal data governance framework should be introduced, requiring data-sharing commitments, public-interest obligations (e.g., pricing conditions or access guarantees), or reinvestment in local research infrastructure as prerequisites for regulatory benefits.

Additionally, continuous improvement of the regulatory structure is necessary. Keeping pace with technological development and clinical advances not only encourages Taiwanese companies to persist in innovation but also provides Taiwanese people with the opportunity to benefit from the latest developments.

3. Build a Sustainable System for CGT

Currently, the raw materials for CGT development and preparation are all imported, resulting in high costs for Taiwanese manufacturers. The government should create policies that encourage companies to engage more in relevant technologies surrounding the CGT supply chain, thereby building a strong ecosystem for the CGT industry within Taiwan.

Additionally, the current outcome-based payment system protects patients from uncertain treatment results, but it poses a significant drawback for manufacturers. Creating a mechanism that incorporates commercial insurance more into the payment system can help share the risk and financial burden among stakeholders.

Without a doubt, the government should remain vigilant towards potential risks associated with CGT-oriented payment reforms. These may include moral hazard, such

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as overutilization or inappropriate patient selection under outcome-based schemes, and the possibility of commercial monopolization if access to high-cost therapies becomes concentrated among a few dominant providers. Anticipating such unintended consequences will be essential to designing sustainable and equitable reimbursement frameworks that minimize these risks.

4. Make Taiwan the Next Center of International Medical Services for CGT

Taiwan is renowned for its exceptional quality of medical talent and services. These excellent human capital resources are capable not only of providing significant potential for the research and development of CGT technologies but also of building an industrial chain for CGT, which, at this stage, is still highly dependent on human services to link the entire process. A premature model has emerged since RASMET, which provides a good foundation for the industry to continue developing.

The government and industries should collaborate to develop exportable CGT service models, leveraging Taiwan's strengths in clinical expertise and CDMO capacity. Beyond technical platforms, Taiwan has the potential to offer integrated CGT delivery solutions, including standardized clinical workflows, regulatory expertise, and scalable manufacturing protocols, that could serve as a template for other emerging markets. These insights could inform decision-making for policymakers, hospital administrators, and biotech investors, facilitating a coherent ecosystem for Taiwan's CGT development.

Meanwhile, companies should also leverage Taiwan's clinical and biomedical strengths by cultivating an environment conducive to translational research, fostering collaboration between hospitals and biotech firms, and positioning Taiwan as a hub for clinical trials and manufacturing.

By addressing both systemic bottlenecks and global positioning, Taiwan can

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transform its CGT sector from a follower in technology adoption into a leader in integrated delivery and innovation strategy.

5.3 Study Limitations and Recommendations for Future Research

This study is subject to several limitations:

1. Patent analysis was limited to US-issued patents, which may have introduced a regional bias. The global innovation landscape, particularly from regions like China, the EU, and Japan, may not have been fully captured, potentially underestimating their contributions or alternative technological trajectories.
2. The analysis of approved CGTs and payment systems relied primarily on publicly available secondary data and a small number of expert interviews. The limited sample size and geographic scope of the interviewees may affect the generalizability of the findings.
3. Clinical trial data were retrieved exclusively from ClinicalTrials.gov, a US-centric registry. This approach may have excluded trials registered in other national systems, especially for CGTs under development outside the United States.
4. The study did not include primary data on cost-effectiveness or payer decision-making in Taiwan, which would be essential to evaluating the feasibility of various payment innovations or regulatory adaptations in the local context.

Building upon the analytical framework developed in this study, future research could explore the following directions:

1. Assess the regulatory flexibility required to support innovation, especially

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within Taiwan's dual-track approval system. Comparative analysis of fast-track and conditional approval mechanisms across jurisdictions could inform future policy design.

2. Conduct comprehensive economic evaluations, including cost-effectiveness analysis (CEA), budget impact modeling (BIM), and pricing elasticity studies, to support pricing decisions that balance innovation incentives with health system sustainability.
3. Develop operational models to implement outcome-based or milestone-based payment schemes, including real-world data infrastructure, patient tracking systems, and risk-sharing contracts.
4. Investigate mechanisms to integrate CGTs into Taiwan's National Health Insurance (NHI), whether through tailored reimbursement packages, innovative co-payment structures, or supplemental insurance schemes.
5. Examine the long-term policy roadmap for CGT in Taiwan, including whether CGT is positioned as a national strategic industry. This should include assessments of industrial policy, cross-ministerial coordination, and integration into regional biotech value chains.
6. Explore the governance and ethical implications of using real-world evidence (RWE) for both regulatory approval and commercial benefit. Future work should focus on designing equitable data access models, establishing public-benefit requirements, and implementing transparent data stewardship mechanisms.

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REFERENCES

Book

Geels, F. W. (2005). *Technological Transitions And System Innovations: A Co-evolutionary And Socio-technical Analysis*. Edward Elgar Publishing Limited. https://doi.org/https://doi.org/10.1162/jiec.2007.1158a

Book Section

Calleja-Sanz, G., Olivella-Nadal, J., & Solé-Parellada, F. (2020). Technology Forecasting: Recent Trends and New Methods. In *Research Methodology in Management and Industrial Engineering* (pp. 45–69). https://doi.org/10.1007/978-3-030-40896-1_3

Chao, W. Y., Chang, Y. T., Tsai, Y. T., Huang, M. C., Lin, Y. C., Wu, M. M., Chi, J. F., Lin, C. L., Cheng, H. F., & Wu, S. M. (2023). Update on Regulation of Regenerative Medicine in Taiwan. In M. C. Galli (Ed.), *Regulatory Aspects of Gene Therapy and Cell Therapy Products—A Global Perspective* (Vol. 1430, pp. 211–219). Springer. https://doi.org/10.1007/978-3-031-34567-8_12

Cho, Y., & Daim, T. (2013). Technology Forecasting Methods. In *Research and Technology Management in the Electricity Industry* (pp. 67–112). https://doi.org/10.1007/978-1-4471-5097-8_4

Dalal, V., Lata, H., Kharkwal, G., & Jotwani, G. (2023). Regulation of Clinical Research for Cellular and Gene Therapy Products in India. In M. C. Galli (Ed.), *Regulatory Aspects of Gene Therapy and Cell Therapy Products—A Global Perspective* (Vol. 1430, pp. 135–154). Springer. https://doi.org/10.1007/978-3-031-34567-8_12

Maruyama, Y., Noda, S., Okudaira, S., Sakurai, A., Okura, N., & Honda, F. (2023a). Regulatory Aspects of Cell and Gene Therapy Products: The Japanese Perspective. In M. C. Galli (Ed.), *Regulatory Aspects of Gene Therapy and Cell Therapy Products—A Global Perspective* (Vol. 1430, pp. 155–180). Springer. https://doi.org/10.1007/978-3-031-34567-8_12

Conference Paper

Mahalatchimy, A., Delage, A., Gilbert, L.-S., Kuo, H.-Y., Roby, V., & Chabannon, C. (2024, October, 2024). *Real access to ATMPs: the cost issue* European Society of Gene & Cell Therapy 2024, Rome, Italy. https://shs.hal.science/halshs-04842702v1

Government Document

Centers for Medicare and Medicaid Services. *Decision memo for chimeric antigen receptor (CAR) T-cell therapy for cancers*. Centers for Medicare & Medicaid Services. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=291

Centers for Medicare and Medicaid Services. (December 21, 2020). *Establishing Minimum Standards in Medicaid State Drug Utilization Review (DUR) and Supporting Value-Based Purchasing (VBP) for Drugs Covered in Medicaid, Revising Medicaid Drug Rebate and Third Party Liability (TPL) Requirements*

doi:10.6342/NTU202502665

(CMS 2482-F) Final Reg. Retrieved April 4 from https://www.cms.gov/newsroom/fact-sheets/establishing-minimum-standards-medicaid-state-drug-utilization-review-dur-and-supporting-value-based-0

Centers for Medicare and Medicaid Services. (September 10, 2024). *Medicare Coverage of Items and Services*. Retrieved April 5 from https://www.cms.gov/cms-guide-medical-technology-companies-and-other-interested-parties/coverage/medicare-coverage-items-and-services

Centers for Medicare and Medicaid Services. (n.d.). *Cell and Gene Therapy (CGT) Access Model*. U.S. Department of Health and Human Services. Retrieved April 4 from https://www.cms.gov/priorities/innovation/innovation-models/cgt

Centers for Medicare and Medicaid Services. (n.d.). *Parts of Medicare*. https://www.medicare.gov/basics/get-started-with-medicare/medicare-basics/parts-of-medicare

Department of Medical Affairs. (August 17, 2010). *Wei fu bu "Xi bao Zhi liaoo Ji shu Zi xun Zhuan qu" Gai ban Shang xian Ti gong Xi bao Zhil iaoo Zheng que Wan zheng Zi xun Yi Bao zhang Min zhong Quan yi [The Ministry of Health and Welfare's "Cell Therapy Technology Information Zone" has been revised and launched to provide accurate and complete information on cell therapy to protect the rights of the public]*. Ministry of Health and Welfare. Retrieved July 28 from https://www.mohw.gov.tw/cp-4628-55268-1.html

Department of Medical Affairs. (June 4, 2024). *Lì fǎ yuàn sān dú tōng guò "Zài shēng yī liáo zhì jì tiáo lì", jiā huì bìng rén bìng cù jìn zài shēng yī liáo chǎn yè fā zhǎn [The Legislative Yuan has passed the third reading of the "Regenerative Medicine Products Act," benefiting patients and promoting the development of the regenerative medicine industry]*. Ministry of Health and Welfare. Retrieved May 30 from https://www.mohw.gov.tw/cp-16-78936-1.html

Department of Medical Affairs. (June 4, 2024). *Lì fǎ yuàn sān dú tōng guò 「zài shēng yī liáo fǎ 」kāi qǐ zài shēng yī liáo xīn lǐ chéng [The Legislative Yuan passed the "Regenerative Medicine Act" in the third reading, opening a new milestone in regenerative medicine]*. Ministry of Health and Welfare. Retrieved May 30 from https://www.mohw.gov.tw/cp-16-78933-1.html

Department of Statistics. (n.d.). *guó mín yī liáo bǎo jiàn zhī chū [National Health Expenditure]*. Department of Statistics, Ministry of Health and Welfare Retrieved from https://dep.mohw.gov.tw/DOS/lp-5071-113.html

European Medicines Agency. (n.d.). *Accelerated assessment*. European Medicines Agency. Retrieved June 24 from https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/accelerated-assessment

Advanced therapy medicinal products: Overview, (n.d.–b). https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview

European Medicines Agency. (n.d.). *Conditional marketing authorisation*. European Medicines Agency. Retrieved June 24 from https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation

European Medicines Agency. (n.d.). *Download medicine data*. European Medicines Agency. Retrieved June 24 from https://www.ema.europa.eu/en/medicines/download-medicine-data

European Medicines Agency. (n.d.). *Orphan designation: Overview*. Retrieved June 24 from https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview#orphan-medicine-incentives-11926

doi:10.6342/NTU202502665

European Medicines Agency. (n.d.). *Pre-authorisation guidance*. European Medicines Agency. Retrieved June 24 from https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/pre-authorisation-guidance
European Medicines Agency. (n.d.). *PRIME: priority medicines*. European Medicines Agency. Retrieved June 26 from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines
Fukuda, T. (2018). *Drug Pricing in Japan*. Retrieved from https://www.ispor.org/docs/default-source/conference-ap-2018/ispor_ap-ip1-20180909-fukuda.pdf?sfvrsn=84310438_0
Ministry of Health, Labour and Welfare, Japan. (2024a). *Partial Revision of "Designation of Orphan Drugs etc."*. Tokyo: Ministry of Health, Labour and Welfare
Ministry of Health, Labour and Welfare, Japan. (2024b). *Questions and Answers (Q&A) for Designation of Orphan Drugs etc.* Tokyo: Ministry of Health, Labour and Welfare
Ministry of Health, Labour and Welfare, Japan. (n.d.). *Strategy of SAKIGAKE*. Ministry of Health, Labour and Welfare. Retrieved June 24 from https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html
Ministry of Health and Welfare. (April 12, 2024). *Huí yìng "Tè guǎn bàn fǎ shàng lù fāng jiān shōu fèi luàn, mín tuán yōu bìng yǒu lún dài zāi féi yáng" bào dǎo: Mù qián yǐ yǒu yán jǐn de guī fàn, jiāng yáng gé bǎ guān yǐ què bǎo mínz hòng quán yì. [Response to the report titled "Unregulated Charges Following the Implementation of the Special Regulation—Concern That Patients May Be Exploited": There are already stringent regulations in place, and strict oversight will be enforced to ensure the protection of public interests.]*. Ministry of Health and Welfare. Retrieved June 25 from https://www.mohw.gov.tw/cp-4343-48346-1.html
Ministry of Health and Welfare. (n.d.). *Xī bāo zhì liáo jì shù zī xùn zhuān qū [Cell Therapy Technology Information Portal]*. Ministry of Health and Welfare. Retrieved June 26 from https://celltherapy.mohw.gov.tw
National Health Insurance Administration. (2023a). *quán mín jiàn kāng bǎo xiǎn yào wù gěi fù xiàng mù jí zhī fù biāo zhǔn gòng tóng nǐ dìng huì yì yào pǐn bù fèn dì 62 cì huì yì jì lù [Joint drafting meeting on the National Health Insurance drug benefit items and payment standards-Minutes of the 62nd meeting on drugs]*. Ministry of Health and Welfare Retrieved from https://www.nhi.gov.tw/ch/dl-11918-b31caa68067a4e9e837077d53cd06c3d-1.pdf
National Health Insurance Administration. (2023b). *quán mín jiàn kāng bǎo xiǎn yào wù gěi fù xiàng mù jí zhī fù biāo zhǔn gòng tóng nǐ dìng huì yì yào pǐn bù fèn dì 63 cì huì yì jì lù [Joint drafting meeting on the National Health Insurance drug benefit items and payment standards-Minutes of the 63rd meeting on drugs]*. Ministry of Health and Welfare Retrieved from https://www.nhi.gov.tw/ch/dl-47931-f4e517142a5246cab22a10f201723df1-1.pdf
National Health Insurance Administration. (February 15, 2024). *Universal Health Coverage in Taiwan*. National Health Insurance Administration, Taiwan. Retrieved May 31 from https://www.nhi.gov.tw/en/cp-5-96705-57-2.html
National Health Insurance Administration. (n.d.). *NHI Timeline*. National Health Insurance Administration, Taiwan. Retrieved May 31 from https://www.nhi.gov.tw/en/mp-2.html
Pharmaceuticals and Medical Devices Agency, Japan. (n.d.). *List of Approved Products*. Pharmaceuticals and Medical Devices Agency. Retrieved June 24 from

doi:10.6342/NTU202502665

https://www.pmda.go.jp/english/review-services/reviews/approved-information/0002.html
Pharmaceuticals and Medical Devices Agency, Japan. (n.d.). *Regenerative Medical Products*. https://www.pmda.go.jp/english/review-services/reviews/0003.html
Pharmaceuticals and Medical Devices Agency, Japan. (n.d.). *Strategy of SAKIGAKE by MHLW*. Pharmaceuticals and Medical Devices Agency. Retrieved June 24 from https://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0001.html
Pharmaceuticals and Medical Devices Agency, Japan. (n.d.). *Yakka kijun shūsai hinmoku risuto oyobi kōhatsu iyakuhin ni kansuru jōhō ni tsuite (Reiwa nana-nen san-gatsu sanjūichi-nichi made) [Information on the Drug Price List and Generic Drugs (until March 31, 2025)]*. Ministry of Health, Labour and Welfare, Japan,. Retrieved June 24 from https://www.mhlw.go.jp/topics/2024/04/tp20240401-01.html
Taiwan Intellectual Property Office. (January 10, 2025). *quán qiú zhuān lì jiǎn suǒ xì tǒng GPSSgōng néng jiè shào [Introduction to the functions of the Global Patent Search System GPSS]*. Taiwan Intellectual Property Office (TIPO). Retrieved April 29 from https://www.tipo.gov.tw/tw/cp-1018-946868-eaf5b-1.html
US Food and Drug Administration. (January 4, 2018). *Breakthrough Therapy*. Retrieved June 28 from https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy
US Food and Drug Administration. (March 20, 2023). *Cellular & Gene Therapy Products*. Retrieved March 18 from https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products
US Food and Drug Administration. (July 21, 2023). *Regenerative Medicine Advanced Therapy Designation*. U.S. Food and Drug Administration. Retrieved June 28 from https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation
US Food and Drug Administration. (August 12, 2024). *Designating an Orphan Product: Drugs and Biological Products*. U.S. Food and Drug Administration. Retrieved June 28 from https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products
US Food and Drug Administration. (September 27, 2024). *Rare Pediatric Disease Designation and Priority Review Voucher Programs*. U.S. Food and Drug Administration. Retrieved June 28 from https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-designation-and-priority-review-voucher-programs
US Food and Drug Administration. (May 13, 2025). *CBER Regenerative Medicine Advanced Therapy (RMAT) Approvals*. U.S. Food & Drug Administration. Retrieved June 28 from https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cber-regenerative-medicine-advanced-therapy-rmat-approvals
US Food and Drug Administration. (January 13, 2025). *Fast Track Designation Requests*. U.S. Food and Drug Administration. Retrieved June 28 from https://www.fda.gov/drugs/ind-activity/fast-track-designation-requests
US Food and Drug Administration. (May 15, 2925). *Approved Cellular and Gene Therapy Products*. U.S. Food and Drug Administration. Retrieved June 28 from https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Journal Article

doi:10.6342/NTU202502665

Ahumada-Ayala, M., Aguilar-López, R., González-Stoylov, N., Palacio-Sosa, E., Cervantes-Barragán, D. E., & Fernández-Hernández, L. (2023). Editing the Human Genome with CRISPR/Cas: A Review of its Molecular Basis, Current Clinical Applications, and Bioethical Implications. *REVISTA DE INVESTIGACIÓN CLÍNICA*, *75*(1), 13–28. https://doi.org/10.24875/RIC.22000252

Allen, J., Berry, D., Cook, F., Hume, A., Rouce, R., Srirangam, A., Wellman, J., & McCombs, C. (2023). Medicaid coverage practices for approved gene and cell therapies: Existing barriers and proposed policy solutions. *Mol Ther Methods Clin Dev*, *29*, 513–521. https://doi.org/10.1016/j.omtm.2023.05.015

Anderson, P., & Tushman, M. L. (1990). Technological Discontinuities and Dominant Designs: A Cyclical Model of Technological Change. *Administrative Science Quarterly*, *35*(4). https://doi.org/10.2307/2393511

Arato, T., & Nomura, K. (2024). Cell and gene therapy approvals in Japan and the need for international harmonization. *Nat Biotechnol*, *42*(1), 13–17. https://doi.org/10.1038/s41587-023-02053-7

Au, H. K. E., Isalan, M., & Mielcarek, M. (2021). Gene Therapy Advances: A Meta-Analysis of AAV Usage in Clinical Settings. *Front Med (Lausanne)*, *8*. https://doi.org/10.3389/fmed.2021.809118

Awasthi, R., Maier, H. J., Zhang, J., & Lim, S. (2023). Kymriah(R) (tisagenlecleucel) - An overview of the clinical development journey of the first approved CAR-T therapy. *Hum Vaccin Immunother*, *19*(1). https://doi.org/10.1080/21645515.2023.2210046

Azuma, K. (2015). Regulatory Landscape of Regenerative Medicine in Japan. *Current Stem Cell Reports*, *1*(2), 118–128. https://doi.org/10.1007/s40778-015-0012-6

Bach, P. B., Giralt, S. A., & Saltz, L. B. (2017). FDA Approval of Tisagenlecleucel: Promise and Complexities of a $475,000 Cancer Drug. *Jama*, *318*(19), 1861–1862. https://doi.org/10.1001/jama.2017.15218

Baghbaderani, B. A., Syama, A., Sivapatham, R., Pei, Y., Mukherjee, O., Fellner, T., Zeng, X., & Rao, M. S. (2016). Detailed Characterization of Human Induced Pluripotent Stem Cells Manufactured for Therapeutic Applications. *Stem Cell Rev Rep*, *12*(4), 394–420. https://doi.org/10.1007/s12015-016-9662-8

Bald, T., Krummel, M. F., Smyth, M. J., & Barry, K. C. (2020). The NK cell-cancer cycle: advances and new challenges in NK cell-based immunotherapies. *Nat Immunol*, *21*(8), 835–847. https://doi.org/10.1038/s41590-020-0728-z

Barrangou, R., & Doudna, J. A. (2016). Applications of CRISPR technologies in research and beyond. *Nat Biotechnol*, *34*(9), 933–941. https://doi.org/10.1038/nbt.3659

Barry, F. P. (2003). Biology and clinical applications of mesenchymal stem cells. *Birth Defects Res C Embryo Today*, *69*(3), 250–256. https://doi.org/10.1002/bdrc.10021

Beinfeld, M. T., Rucker, J. A., Jenkins, N. B., de Breed, L. A., & Chambers, J. D. (2023). Variation in Medicaid and commercial coverage of cell and gene therapies. *Health Policy Open*, *5*. https://doi.org/10.1016/j.hpopen.2023.100103

Berry, D., Hickey, C., Kahlman, L., Long, J., Markus, C., & McCombs, C. K. (2025). Ensuring patient access to gene therapies for rare diseases: Navigating reimbursement and coverage challenges. *Mol Ther Methods Clin Dev*, *33*(1). https://doi.org/10.1016/j.omtm.2024.101403

Bing, S. J., Justesen, S., Wu, W. W., Sajib, A. M., Warrington, S., Baer, A., Thorgrimsen, S., Shen, R. F., & Mazor, R. (2022). Differential T cell immune responses to deamidated adeno-associated virus vector. *Mol Ther Methods Clin Dev*, *24*, 255–267. https://doi.org/10.1016/j.omtm.2022.01.005

doi:10.6342/NTU202502665

Bobis, S., Jarocha, D., & Majka, M. (2006). Mesenchymal stem cells: characteristics and clinical applications. *Folia Histochemica et Cytobiologica*, *44*(4), 215–230. https://doi.org/10.5603/4554

Borrás, S., & Edquist, C. (2013). The choice of innovation policy instruments. *Technological Forecasting and Social Change*, *80*(8), 1513–1522. https://doi.org/10.1016/j.techfore.2013.03.002

Burki, T. K. (2019). Drug pricing in the USA. *Lancet Respir Med*, *7*(11), 937. https://doi.org/10.1016/S2213-2600(19)30332-7

Caligiuri, M. A. (2008). Human natural killer cells. *Blood*, *112*(3), 461–469. https://doi.org/10.1182/blood-2007-09-077438

Callenbach, M. H. E., Goettsch, W. G., Mantel-Teeuwisse, A. K., & Trusheim, M. (2024). Creating win-win-win situations with managed entry agreements? Prioritizing gene and cell therapies within the window of opportunity. *Drug Discov Today*, *29*(7). https://doi.org/10.1016/j.drudis.2024.104048

Caracciolo, D., Mancuso, A., Polera, N., Froio, C., D'Aquino, G., Riillo, C., Tagliaferri, P., & Tassone, P. (2023). The emerging scenario of immunotherapy for T-cell Acute Lymphoblastic Leukemia: advances, challenges and future perspectives. *Exp Hematol Oncol*, *12*(1). https://doi.org/10.1186/s40164-022-00368-w

Carvalho, M., Sepodes, B., & Martins, A. P. (2021). Patient access to gene therapy medicinal products: a comprehensive review. *BMJ Innovations*, *7*(1), 123–134. https://doi.org/10.1136/bmjinnov-2020-000425

Cerneckis, J., Cai, H., & Shi, Y. (2024). Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal Transduct Target Ther*, *9*(1). https://doi.org/10.1038/s41392-024-01809-0

Chancellor, D., Barrett, D., Nguyen-Jatkoe, L., Millington, S., & Eckhardt, F. (2023). The state of cell and gene therapy in 2023. *Mol Ther*, *31*(12), 3376–3388. https://doi.org/10.1016/j.ymthe.2023.11.001

Chehelgerdi, M., Chehelgerdi, M., Khorramian-Ghahfarokhi, M., Shafieizadeh, M., Mahmoudi, E., Eskandari, F., Rashidi, M., Arshi, A., & Mokhtari-Farsani, A. (2024). Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. *Mol Cancer*, *23*(1), 9. https://doi.org/10.1186/s12943-023-01925-5

Cheng, X., Fan, S., & Xianfa, C. W. a. (2020). CRISPR/Cas9 for cancer treatment: technology, clinical applications and challenges. *Briefings in Functional Genomics*, *19*(3), 209–214. https://doi.org/10.1093/bfgp/elaa001

Conti, R. M., Demartino, P., Gruber, J., Lo, A. W., Sun, Y., & Wu, J. (2025). Innovative Insurance to Improve US Patient Access to Cell and Gene Therapy. *Milbank Q*, *103*(1), 32–51. https://doi.org/10.1111/1468-0009.12728

Coppens, D. G. M., de Wilde, S., Guchelaar, H. J., De Bruin, M. L., Leufkens, H. G. M., Meij, P., & Hoekman, J. (2018). A decade of marketing approval of gene and cell-based therapies in the United States, European Union and Japan: An evaluation of regulatory decision-making. *Cytotherapy*, *20*(6), 769–778. https://doi.org/10.1016/j.jcyt.2018.03.038

Cring, M. R., & Sheffield, V. C. (2022). Gene therapy and gene correction: targets, progress, and challenges for treating human diseases. *Gene Ther*, *29*(1-2), 3–12. https://doi.org/10.1038/s41434-020-00197-8

Dash, C. P., Sonowal, D., Dhaka, P., Yadav, R., Chettri, D., Satapathy, B. P., Sheoran, P., Uttam, V., Jain, M., & Jain, A. (2024). Antitumor activity of genetically engineered NK-cells in non-hematological solid tumor: a comprehensive review. *Front Immunol*, *15*. https://doi.org/10.3389/fimmu.2024.1390498

doi:10.6342/NTU202502665

Denise T Kruzikas, Malone, D. C., Pham, S., Reinsch, T. K., & Akehurst, R. (2020). HTA and economics in the United States: a systematic review of ICER reports to evaluate trends, identify factors associated with recommendations, and understand implications. *JMCP*, *26*(12), 1548–1557. https://doi.org/10.18553/jmcp.2020.26.12.1548

Desmet, T., Michelsen, S., Van den Brande, E., Van Dyck, W., Simoens, S., & Huys, I. (2024). Towards implementing new payment models for the reimbursement of high-cost, curative therapies in Europe: insights from semi-structured interviews. *Front Pharmacol*, *15*. https://doi.org/10.3389/fphar.2024.1397531

Dias, J., Garcia, J., Agliardi, G., & Roddie, C. (2024). CAR-T cell manufacturing landscape-Lessons from the past decade and considerations for early clinical development. *Mol Ther Methods Clin Dev*, *32*(2). https://doi.org/10.1016/j.omtm.2024.101250

Dickinson, M. J., Barba, P., Jager, U., Shah, N. N., Blaise, D., Briones, J., Shune, L., Boissel, N., Bondanza, A., Mariconti, L., Marchal, A. L., Quinn, D. S., Yang, J., Price, A., Sohoni, A., Treanor, L. M., Orlando, E. J., Mataraza, J., Davis, J.,…Flinn, I. W. (2023). A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development. *Cancer Discov*, *13*(9), 1982–1997. https://doi.org/10.1158/2159-8290.CD-22-1276

Dosi, G. (1982). Technological paradigms and technological trajectories: A suggested interpretation of the determinants and directions of technical change. *Research Policy*, *11*, 147–162. https://doi.org/0048-7333/82/0000-0000

Doss, M. X., & Sachinidis, A. (2019). Current Challenges of iPSC-Based Disease Modeling and Therapeutic Implications. *Cells*, *8*(5). https://doi.org/10.3390/cells8050403

Edler, J., & Georghiou, L. (2007). Public procurement and innovation—Resurrecting the demand side. *Research Policy*, *36*(7), 949–963. https://doi.org/10.1016/j.respol.2007.03.003

El-Kadiry, A. E., Rafei, M., & Shammaa, R. (2021). Cell Therapy: Types, Regulation, and Clinical Benefits. *Front Med (Lausanne)*, *8*. https://doi.org/10.3389/fmed.2021.756029

Elverum, K., & Whitman, M. (2020). Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine. *Gene Therapy*, *27*(12), 537–544. https://doi.org/10.1038/s41434-019-0074-7

Fang, F., Wang, W., Chen, M., Tian, Z., & Xiao, W. (2019). Technical advances in NK cell-based cellular immunotherapy. *Cancer Biol Med*, *16*(4), 647–654. https://doi.org/10.20892/j.issn.2095-3941.2019.0187

Fellmann, C., Gowen, B. G., Lin, P. C., Doudna, J. A., & Corn, J. E. (2017). Cornerstones of CRISPR-Cas in drug discovery and therapy. *Nat Rev Drug Discov*, *16*(2), 89–100. https://doi.org/10.1038/nrd.2016.238

Fischer, P., Reiss, T., Mahlich, J., Gicquel, E., Aichinger, H., Pullmann, L., & Bratan, T. (2023). Unlocking the value of innovative medicines: Insights from the advanced therapy medicinal products (ATMP) innovation systems in Germany and Sweden. *Health Policy and Technology*, *12*(2). https://doi.org/10.1016/j.hlpt.2023.100744

Foss, D. V., Hochstrasser, M. L., & Wilson, R. C. (2019). Clinical applications of CRISPR-based genome editing and diagnostics. *Transfusion*, *59*(4), 1389–1399. https://doi.org/10.1111/trf.15126

Gambella, M., Carlomagno, S., Raiola, A. M., Giannoni, L., Ghiggi, C., Setti, C., Giordano, C., Luchetti, S., Serio, A., Bo, A., Falco, M., Della Chiesa, M.,

doi:10.6342/NTU202502665

Angelucci, E., & Sivori, S. (2022). CD19-Targeted Immunotherapies for Diffuse Large B-Cell Lymphoma. *Front Immunol*, *13*. https://doi.org/10.3389/fimmu.2022.837457

Gao, L., Porter, A. L., Wang, J., Fang, S., Zhang, X., Ma, T., Wang, W., & Huang, L. (2013). Technology life cycle analysis method based on patent documents. *Technological Forecasting and Social Change*, *80*(3), 398–407. https://doi.org/10.1016/j.techfore.2012.10.003

Guo, N., Liu, J. B., Li, W., Ma, Y. S., & Fu, D. (2022). The power and the promise of CRISPR/Cas9 genome editing for clinical application with gene therapy. *J Adv Res*, *40*, 135–152. https://doi.org/10.1016/j.jare.2021.11.018

Hampson, G., Towse, A., Pearson, S. D., Dreitlein, W. B., & Henshall, C. (2018). Gene therapy: evidence, value and affordability in the US health care system [White Paper]. *Journal of Comparative Effectiveness Research*, *7*(1), 16–28. https://doi.org/10.2217/cer-2017-0068

Hartmann, J., Schussler-Lenz, M., Bondanza, A., & Buchholz, C. J. (2017). Clinical development of CAR T cells-challenges and opportunities in translating innovative treatment concepts. *EMBO Mol Med*, *9*(9), 1183–1197. https://doi.org/10.15252/emmm.201607485

Horrow, C., & Kesselheim, A. S. (2023). Confronting High Costs And Clinical Uncertainty: Innovative Payment Models For Gene Therapies. *Health Aff (Millwood)*, *42*(11), 1532–1540. https://doi.org/10.1377/hlthaff.2023.00527

Huang, Y., Li, R., Zou, F., Jiang, L., Porter, A. L., & Zhang, L. (2022). Technology life cycle analysis: From the dynamic perspective of patent citation networks. *Technological Forecasting and Social Change*, *181*. https://doi.org/10.1016/j.techfore.2022.121760

Iglesias-Lopez, C., Agusti, A., Vallano, A., & Obach, M. (2023). Financing and Reimbursement of Approved Advanced Therapies in Several European Countries. *Value Health*, *26*(6), 841–853. https://doi.org/10.1016/j.jval.2022.12.014

Issa, S. S., Shaimardanova, A. A., Solovyeva, V. V., & Rizvanov, A. A. (2023). Various AAV Serotypes and Their Applications in Gene Therapy: An Overview. *Cells*, *12*(5). https://doi.org/10.3390/cells12050785

Jogalekar, M. P., Rajendran, R. L., Khan, F., Dmello, C., Gangadaran, P., & Ahn, B. C. (2022). CAR T-Cell-Based gene therapy for cancers: new perspectives, challenges, and clinical developments. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.925985

Jorgensen, J., Hanna, E., & Kefalas, P. (2020). Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *J Mark Access Health Policy*, *8*(1). https://doi.org/10.1080/20016689.2020.1715536

Jorgensen, J., & Kefalas, P. (2015). Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Health Policy*, *3*. https://doi.org/10.3402/jmahp.v3.29321

Jorgensen, L. V., Christensen, E. B., Barnkob, M. B., & Barington, T. (2025). The clinical landscape of CAR NK cells. *Exp Hematol Oncol*, *14*(1), 46. https://doi.org/10.1186/s40164-025-00633-8

June, C. H., O'Connor, R. S., Kawalekar, O. U., Saba Ghassemi, & Milone, M. C. (2018). CAR T cell immunotherapy for human cancer. *Science*, *359*, 1361–1365. https://doi.org/10.1126/science.aar6711

Kang, L., Jin, S., Wang, J., Lv, Z., Xin, C., Tan, C., Zhao, M., Wang, L., & Liu, J. (2023). AAV vectors applied to the treatment of CNS disorders: Clinical status and

doi:10.6342/NTU202502665

challenges. *J Control Release*, *355*, 458–473. https://doi.org/10.1016/j.jconrel.2023.01.067

Kang, S. Y., Bai, G., DiStefano, M. J., Socal, M. P., Yehia, F., & Anderson, G. F. (2020). Comparative Approaches to Drug Pricing. *Annu Rev Public Health*, *41*, 499–512. https://doi.org/10.1146/annurev-publhealth-040119-094305

Kast, J., Nozohouri, S., Zhou, D., Yago, M. R., Chen, P. W., Ahamadi, M., Dutta, S., & Upreti, V. V. (2022). Recent advances and clinical pharmacology aspects of Chimeric Antigen Receptor (CAR) T-cellular therapy development. *Clin Transl Sci*, *15*(9), 2057–2074. https://doi.org/10.1111/cts.13349

Kim, G., & Bae, J. (2017). A novel approach to forecast promising technology through patent analysis. *Technological Forecasting and Social Change*, *117*, 228–237. https://doi.org/10.1016/j.techfore.2016.11.023

Kishimoto, T. K., & Samulski, R. J. (2022). Addressing high dose AAV toxicity - 'one and done' or 'slower and lower'? *Expert Opin Biol Ther*, *22*(9), 1067–1071. https://doi.org/10.1080/14712598.2022.2060737

Kobolak, J., Dinnyes, A., Memic, A., Khademhosseini, A., & Mobasheri, A. (2016). Mesenchymal stem cells: Identification, phenotypic characterization, biological properties and potential for regenerative medicine through biomaterial micro-engineering of their niche. *Methods*, *99*, 62–68. https://doi.org/10.1016/j.ymeth.2015.09.016

KOÇKAYA, G. v., OĞUZHAN, G. l., ÜLGER, F. M., & ÇAM, K. (2020). Health Policies About Gene & Cell Therapies in France, Germany, Italy, Unıted Kıngdom, Spain, Portugal And Turkey. *Eurasian Journal of Health Technology Assessment*, *4*(2), 49–67.

Kohn, D. B., Chen, Y. Y., & Spencer, M. J. (2023). Successes and challenges in clinical gene therapy. *Gene Ther*, *30*(10-11), 738–746. https://doi.org/10.1038/s41434-023-00390-5

Lai, R. C., Chen, T. S., & Lim, S. K. (2011). Mesenchymal stem cell exosome: a novel stem cell-based therapy for cardiovascular disease. *Regen Med*, *6*(4), 481–492. https://doi.org/10.2217/rme.11.35

Lee, C., Kwon, O., Kim, M., & Kwon, D. (2018). Early identification of emerging technologies: A machine learning approach using multiple patent indicators. *Technological Forecasting and Social Change*, *127*, 291–303. https://doi.org/10.1016/j.techfore.2017.10.002

Lee, S., & Lee, J. H. (2023). Cell and gene therapy regulatory, pricing, and reimbursement framework: With a focus on South Korea and the EU. *Front Public Health*, *11*. https://doi.org/10.3389/fpubh.2023.1109873

Li, Y. R., Lyu, Z., Chen, Y., Fang, Y., & Yang, L. (2024). Frontiers in CAR-T cell therapy for autoimmune diseases. *Trends Pharmacol Sci*, *45*(9), 839–857. https://doi.org/10.1016/j.tips.2024.07.005

Lim, J. M., & Kim, H. H. (2022). Basic Principles and Clinical Applications of CRISPR-Based Genome Editing. *Yonsei Med J*, *63*(2), 105–113. https://doi.org/10.3349/ymj.2022.63.2.105

Ling, Q., Herstine, J. A., Bradbury, A., & Gray, S. J. (2023). AAV-based in vivo gene therapy for neurological disorders. *Nat Rev Drug Discov*, *22*(10), 789–806. https://doi.org/10.1038/s41573-023-00766-7

Liu, I. T. T., Lalani, H. S., & Kesselheim, A. S. (2024). Administrative action on drug pricing: Lessons and opportunities for the Center for Medicare and Medicaid Innovation. *J Manag Care Spec Pharm.*, *30*(3), 290–301. https://doi.org/10.18553/jmcp.2023.23208

doi:10.6342/NTU202502665

Liu, S., Galat, V., Galat, Y., Lee, Y. K. A., Wainwright, D., & Wu, J. (2021). NK cell-based cancer immunotherapy: from basic biology to clinical development. *J Hematol Oncol*, *14*(7). https://doi.org/10.1186/s13045-020-01014-w

Lopata, E., Terrone, C., & Gopalan, A. (2023). Opportunities and challenges surrounding financial models for high-investment medications A survey of access decision-makers and employers. *Journal of Managed Care & Specialty Pharmacy*, *29*(7), 782–790. https://doi.org/10.18553/jmcp.2023.22436

Lotfy, A., AboQuella, N. M., & Wang, H. (2023). Mesenchymal stromal/stem cell (MSC)-derived exosomes in clinical trials. *Stem Cell Research & Therapy*, *14*(66). https://doi.org/https://doi.org/10.1186/s13287-023-03287-7

Lysaght, T. (2017). Accelerating regenerative medicine: the Japanese experiment in ethics and regulation. *Regen Med*, *12*(6), 657–668. https://doi.org/10.2217/rme-2017-0038

Maeda, D., Yamaguchi, T., Ishizuka, T., Hirata, M., Takekita, K., & Sato, D. (2015). Regulatory Frameworks for Gene and Cell Therapies in Japan. *Adv Exp Med Biol*, *871*, 147–162. https://doi.org/10.1007/978-3-319-18618-4_8

Makita, S., Yoshimura, K., & Tobinai, K. (2017). Clinical development of anti-CD19 chimeric antigen receptor T-cell therapy for B-cell non-Hodgkin lymphoma. *Cancer Sci*, *108*(6), 1109–1118. https://doi.org/10.1111/cas.13239

Maruyama, Y., Kasai, M., Oyama, K., & Chikazawa, K. (2018). Experiences from Japan – SAKIGAKE Designation System for Regenerative Medical Products. *Cell Gene Therapy Insights*, *4*(6), 545–554. https://doi.org/10.18609/cgti.2018.045

Maruyama, Y., Noda, S., Okudaira, S., Sakurai, A., Okura, N., & Honda, F. (2023b). Regulatory Aspects of Cell and Gene Therapy Products: The Japanese Perspective. *Adv Exp Med Biol*, *1430*, 155–179. https://doi.org/10.1007/978-3-031-34567-8_9

McGee, J., & Thomas, H. (1986). Strategic groups: Theory, research and taxonomy. *Strategic Management Journal*, *7*(2), 141–160. https://doi.org/10.1002/smj.4250070204

Mohan, R., Reckelbus, M., & Borry, P. (2025). Regional disparities in access to gene therapies in the European Union, the United States, Japan, and China. *Per Med*. https://doi.org/10.1080/17410541.2025.2515002

Morshedzadeh, F., Ghanei, M., Lotfi, M., Ghasemi, M., Ahmadi, M., Najari-Hanjani, P., Sharif, S., Mozaffari-Jovin, S., Peymani, M., & Abbaszadegan, M. R. (2024). An Update on the Application of CRISPR Technology in Clinical Practice. *Mol Biotechnol*, *66*(2), 179–197. https://doi.org/10.1007/s12033-023-00724-z

Myers, J. A., & Miller, J. S. (2021). Exploring the NK cell platform for cancer immunotherapy. *Nat Rev Clin Oncol*, *18*(2), 85–100. https://doi.org/10.1038/s41571-020-0426-7

Naso, M. F., Tomkowicz, B., Perry, W. L., 3rd, & Strohl, W. R. (2017). Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *BioDrugs*, *31*(4), 317–334. https://doi.org/10.1007/s40259-017-0234-5

Negoro, T., Okura, H., & Matsuyama, A. (2017). Induced Pluripotent Stem Cells: Global Research Trends. *Biores Open Access*, *6*(1), 63–73. https://doi.org/10.1089/biores.2017.0013

Nisanov, A. M., Rivera de Jesus, J. A., & Schaffer, D. V. (2025). Advances in AAV capsid engineering: Integrating rational design, directed evolution and machine learning. *Mol Ther*, *33*(5), 1937–1945. https://doi.org/10.1016/j.ymthe.2025.03.056

Okada, K., Miyata, T., & Sawa, Y. (2017). Insurance systems and reimbursement concerning research and development of regenerative medicine in Japan. *Regen Med*, *12*(2), 179–186. https://doi.org/10.2217/rme-2016-0124

doi:10.6342/NTU202502665

Paes, B., Moco, P. D., Pereira, C. G., Porto, G. S., de Sousa Russo, E. M., Reis, L. C. J., Covas, D. T., & Picanco-Castro, V. (2017). Ten years of iPSC: clinical potential and advances in vitro hematopoietic differentiation. *Cell Biol Toxicol*, *33*(3), 233–250. https://doi.org/10.1007/s10565-016-9377-2

Page, A., Chuvin, N., Valladeau-Guilemond, J., & Depil, S. (2024). Development of NK cell-based cancer immunotherapies through receptor engineering. *Cell Mol Immunol*, *21*(4), 315–331. https://doi.org/10.1038/s41423-024-01145-x

Peteraf, M., & Shanley, M. (1998). Getting to Know You: A Theory of Strategic Group Identity. *Strategic Management Journal*, *18*(S1), 165–186. https://doi.org/10.1002/(sici)1097-0266(199707)18:1

Pillai, M., Davies, M. M., & Thistlethwaite, F. C. (2020). Delivery of adoptive cell therapy in the context of the health-care system in the UK: challenges for clinical sites. *Ther Adv Vaccines Immunother*, *8*. https://doi.org/10.1177/2515135520944355

Pittenger, M. F., Discher, D. E., Peault, B. M., Phinney, D. G., Hare, J. M., & Caplan, A. I. (2019). Mesenchymal stem cell perspective: cell biology to clinical progress. *NPJ Regen Med*, *4*(22). https://doi.org/10.1038/s41536-019-0083-6

Poetsch, M. S., Strano, A., & Guan, K. (2022). Human Induced Pluripotent Stem Cells: From Cell Origin, Genomic Stability, and Epigenetic Memory to Translational Medicine. *Stem Cells*, *40*(6), 546–555. https://doi.org/10.1093/stmcls/sxac020

Quinn, C., Ciarametaro, M., Sils, B., Phares, S., & Trusheim, M. (2023). Medicaid best price reforms to enable innovative payment models for cell and gene therapies. *Expert Rev Pharmacoecon Outcomes Res*, *23*(2), 191–203. https://doi.org/10.1080/14737167.2023.2159813

Ramos, C. A., & Dotti, G. (2011). Chimeric antigen receptor (CAR)-engineered lymphocytes for cancer therapy. *Expert Opin Biol Ther*, *11*(7), 855–873. https://doi.org/10.1517/14712598.2011.573476

Rejon-Parrilla, J. C., Espin, J., Garner, S., Kniazkov, S., & Epstein, D. (2023). Pricing and reimbursement mechanisms for advanced therapy medicinal products in 20 countries. *Front Pharmacol*, *14*. https://doi.org/10.3389/fphar.2023.1199500

Riva, L., & Petrini, C. (2019). A few ethical issues in translational research for gene and cell therapy. *J Transl Med*, *17*. https://doi.org/10.1186/s12967-019-02154-5

Ronco, V., Dilecce, M., Lanati, E., Canonico, P. L., & Jommi, C. (2021). Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations? *J Pharm Policy Pract*, *14*(1), 30. https://doi.org/10.1186/s40545-021-00311-0

Sabatini, M. T., & Chalmers, M. (2023). The Cost of Biotech Innovation: Exploring Research and Development Costs of Cell and Gene Therapies. *Pharmaceur Med.*, *37*(5), 365–375. https://doi.org/10.1007/s40290-023-00480-0

Sanchez-Guijo, F., Vives, J., Ruggeri, A., Chabannon, C., Corbacioglu, S., Dolstra, H., Farge, D., Gagelmann, N., Horgan, C., Kuball, J., Neven, B., Rintala, T., Rocha, V., Sanchez-Ortega, I., Snowden, J. A., Zwaginga, J. J., Gnecchi, M., & Sureda, A. (2024). Current challenges in cell and gene therapy: a joint view from the European Committee of the International Society for Cell & Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT). *Cytotherapy*, *26*(7), 681–685. https://doi.org/10.1016/j.jcyt.2024.02.007

Sarv, S., Kahre, T., Vaidla, E., Pajusalu, S., Muru, K., Põder, H., Gross-Paju, K., Ütt, S., Žordania, R., Talvik, I., Õiglane-Shlik, E., Muhu, K., & Õunap, K. (2021). The Birth Prevalence of Spinal Muscular Atrophy: A Population Specific Approach in Estonia. *Frontiers in Genetics*, *12*.

doi:10.6342/NTU202502665

https://doi.org/https://doi.org/10.3389/fgene.2021.796862
Sensebe, L., Krampera, M., Schrezenmeier, H., Bourin, P., & Giordano, R. (2010). Mesenchymal stem cells for clinical application. *Vox Sang*, *98*(2), 93–107. https://doi.org/10.1111/j.1423-0410.2009.01227.x
Shah, N., Chari, A., Scott, E., Mezzi, K., & Usmani, S. Z. (2020). B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia*, *34*(4), 985–1005. https://doi.org/10.1038/s41375-020-0734-z
Shin, M. H., Kim, J., Lim, S. A., Kim, J., Kim, S. J., & Lee, K. M. (2020). NK Cell-Based Immunotherapies in Cancer. *Immune Netw*, *20*(2). https://doi.org/10.4110/in.2020.20.e14
Shukla, V., Enrique Seoane-Vazquez, Fawaz, S., Brown, L., & Rodriguez-Monguio, R. (2019). The Landscape of Cellular and Gene Therapy Products: Authorization, Discontinuations, and Cost. *HUMAN GENE THERAPY CLINICAL DEVELOPMENT*, *30*(3), 102–113. https://doi.org/10.1089/humc.2018.201INTRODUCTION
Shupe, J., Zhang, A., Odenwelder, D. C., & Dobrowsky, T. (2022). Gene therapy: challenges in cell culture scale-up. *Curr Opin Biotechnol*, *75*. https://doi.org/10.1016/j.copbio.2022.102721
Singh, V. K., Kalsan, M., Kumar, N., Saini, A., & Chandra, R. (2015). Induced pluripotent stem cells: applications in regenerative medicine, disease modeling, and drug discovery. *Front Cell Dev Biol*, *3*, 2. https://doi.org/10.3389/fcell.2015.00002
Song, B., Luan, C., & Liang, D. (2023). Identification of emerging technology topics (ETTs) using BERT-based model and sematic analysis: a perspective of multiple-field characteristics of patented inventions (MFCOPIs). *Scientometrics*, *128*(11), 5883–5904. https://doi.org/10.1007/s11192-023-04819-x
Sugai, K., Sumida, M., Shofuda, T., Yamaguchi, R., Tamura, T., Kohzuki, T., Abe, T., Shibata, R., Kamata, Y., Ito, S., Okubo, T., Tsuji, O., Nori, S., Nagoshi, N., Yamanaka, S., Kawamata, S., Kanemura, Y., Nakamura, M., & Okano, H. (2021). First-in-human clinical trial of transplantation of iPSC-derived NS/PCs in subacute complete spinal cord injury: Study protocol. *Regenerative Therapy*, *18*, 321–333. https://doi.org/10.1016/j.reth.2021.08.005
Sun, J. Y., Hu, H. B., Cheng, Y. X., & Lu, X. J. (2020). CRISPR in medicine: applications and challenges. *Brief Funct Genomics*, *19*(3), 151–153. https://doi.org/10.1093/bfgp/elaa011
Tandulje, A. A., Varpe, P. C., Chaugule, P. D., Saji, S., Nizar, F., Raghuvanshi, R. S., & Srivastava, S. (2025). Cell and Gene Therapy Products: Navigating the Regulatory Landscape of Paradigm Approvals in the US (2020 to 2024). *Journal of Pharmaceutical Innovation*, *20*(2). https://doi.org/10.1007/s12247-025-09973-8
Taylor, M., & Taylor, A. (2012). The technology life cycle: Conceptualization and managerial implications. *International Journal of Production Economics*, *140*(1), 541–553. https://doi.org/10.1016/j.ijpe.2012.07.006
Tunis, S., Hanna, E., Neumann, P. J., Toumi, M., Dabbous, O., Drummond, M., Fricke, F. U., Sullivan, S. D., Malone, D. C., Persson, U., & Chambers, J. D. (2021). Variation in market access decisions for cell and gene therapies across the United States, Canada, and Europe. *Health Policy*, *125*(12), 1550–1556. https://doi.org/10.1016/j.healthpol.2021.10.003
Uddin, F., Rudin, C. M., & Sen, T. (2020). CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future. *Front Oncol*, *10*.

doi:10.6342/NTU202502665

https://doi.org/10.3389/fonc.2020.01387
Umemura, M., & Morrison, M. (2021). Comparative lessons in regenerative medicine readiness: learning from the UK and Japanese experience. *Regen Med*, *16*(3), 269–282. https://doi.org/10.2217/rme-2020-0136
Velikanova, R., Wolters, S., Hofstra, H. S., Postma, M. J., & Boersma, C. (2024). Market Access Challenges and Solutions in Cell and Gene Therapy in The Netherlands. *J Mark Access Health Policy*, *12*(3), 181–198. https://doi.org/10.3390/jmahp12030015
Vivier, E., Tomasello, E., Baratin, M., Walzer, T., & Ugolini, S. (2008). Functions of natural killer cells. *Nat Immunol*, *9*(5), 503–510. https://doi.org/10.1038/ni1582
Wagner, D. L., Koehl, U., Chmielewski, M., Scheid, C., & Stripecke, R. (2022). Review: Sustainable Clinical Development of CAR-T Cells - Switching From Viral Transduction Towards CRISPR-Cas Gene Editing. *Front Immunol*, *13*. https://doi.org/10.3389/fimmu.2022.865424
Wang, S., Qu, X., & Zhao, R. C. (2012). Clinical applications of mesenchymal stem cells. *Journal of Hematology & Oncology*, *5*(19). https://doi.org/doi.org/10.1186/1756-8722-5-19
Wang, V., Gauthier, M., Decot, V., Reppel, L., & Bensoussan, D. (2023). Systematic Review on CAR-T Cell Clinical Trials Up to 2022: Academic Center Input. *Cancers (Basel)*, *15*(4). https://doi.org/10.3390/cancers15041003
Wang, Z., & Han, W. (2018). Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomark Res*, *6*, 4. https://doi.org/10.1186/s40364-018-0116-0
Wang, Z., Sun, Y., Shen, R., Tang, X., Xu, Y., Zhang, Y., & Liu, Y. (2022). Global scientific trends on the immunomodulation of mesenchymal stem cells in the 21st century: A bibliometric and visualized analysis. *Front Immunol*, *13*. https://doi.org/10.3389/fimmu.2022.984984
Watanabe, N., Yano, K., Tsuyuki, K., Okano, T., & Yamato, M. (2015). Re-examination of regulatory opinions in Europe: possible contribution for the approval of the first gene therapy product Glybera. *Mol Ther Methods Clin Dev*, *2*. https://doi.org/10.1038/mtm.2014.66
Weber, T. (2021). Anti-AAV Antibodies in AAV Gene Therapy: Current Challenges and Possible Solutions. *Front Immunol*, *12*. https://doi.org/10.3389/fimmu.2021.658399
Wong, C. H., Li, D., Wang, N., Gruber, J., Lo, A. W., & Conti, R. M. (2023). The estimated annual financial impact of gene therapy in the United States. *Gene Ther*, *30*(10-11), 761–773. https://doi.org/10.1038/s41434-023-00419-9
Xu, Z., Yang, J., Xin, X., Liu, C., Li, L., Mei, X., & Li, M. (2023). Merits and challenges of iPSC-derived organoids for clinical applications. *Front Cell Dev Biol*, *11*. https://doi.org/10.3389/fcell.2023.1188905
Yamada, K., Sakai, D., Hiraoka, M., Hatakenaka, K., Hiyoshi, S., Otani, T., Mandai, M., Maeda, T., & Takahashi, M. (2025). Unveiling Willingness to Pay for iPSC-Based Retinal Cell therapy through Discrete Choice Experiments. https://doi.org/http://dx.doi.org/10.2139/ssrn.5178795
Young, P. (2023). Treatment to cure: Advancing AAV gene therapy manufacture. *Drug Discov Today*, *28*(7). https://doi.org/10.1016/j.drudis.2023.103610
Zemplenyi, A., Leonard, J., DiStefano, M. J., Anderson, K. E., Wright, G. C., Mendola, N. D., Nair, K., & McQueen, R. B. (2024). Using Real-World Data to Inform Value-Based Contracts for Cell and Gene Therapies in Medicaid. *Pharmacoeconomics*, *42*(3), 319–328. https://doi.org/10.1007/s40273-023-

doi:10.6342/NTU202502665

01335-x
Zhang, H., Zhan, Q., Huang, B., Wang, Y., & Wang, X. (2022). AAV-mediated gene therapy: Advancing cardiovascular disease treatment. *Front Cardiovasc Med*, *9*. https://doi.org/10.3389/fcvm.2022.952755
Zhang, J. X., & Shugarman, L. R. (2024). Value-based payment and financing for cell and gene therapies: challenges and potential solutions. *J Med Econ*, *27*(1), 678–681. https://doi.org/10.1080/13696998.2024.2346406

Legal Rule or Regulation

Iyaku-hin, iryō-kiki-tō no hinshitsu, yūkōsei oyobi anzensei no kakuho-tō ni kansuru hōritsu [Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices], (1960). https://www.japaneselawtranslation.go.jp/en/laws/view/3213#je_ch6
Regenerative Medicine Act, (2024). https://law.moj.gov.tw/LawClass/LawAll.aspx?pcode=L0020238
quán mín jiàn kāng bǎo xiǎn yào wù jǐ fù xiàng mù jí zhī fù biāo zhǔn [National Health Insurance Drug Benefit Items and Payment Standards], (2025b). https://law.moj.gov.tw/LawClass/LawAll.aspx?PCode=L0060035
Saisei iryō-tō no anzensei no kakuho-tō ni kansuru hōritsu [Act on the Safety of Regenerative Medicine], (2020). https://laws.e-gov.go.jp/law/425AC0000000085#Mp-Ch_1

Magazine Article

Lim, X. H., Ting, D. S. W., Koh, A., & Edited By: Ingrid U. Scott, a. B. J. (2020, June 2020). Retinitis Pigmentosa, Part1: Understanding the Basics. *EyeNet Magazine*, 33–35.
Liu, H. E. (2025, March 2025). Zài shēng yī liáo lì fǎ jí chǎn yè fā zhǎn de lún lǐ yǔ shè huì jī chǔ: yǐ lì yì chōng tú, shěn yì huì duō yuán xìng, bìng rén jiù jì cuò shī yǔ quán yì bǎo hù wéi lì [The ethical and social foundations of regenerative medicine legislation and industry development: Taking conflicts of interest, diversity of review committees, patient relief measures and rights protection as examples]. *The Taiwan Law Review*, (358), 110–126.

Online Database

Chǎn yè jià zhí liàn zī xùn píng tái [Industrial Value Chain Information Platform]. (n.d.).
National Center for Biotechnology Information. (n.d.). *ClinicalTrials.gov*
National Health Insurance Administration. (n.d.–a). *Jiàn bǎo yòng yào pǐn xiàng wǎng lù chá xún fú wù [Online query service for health insurance drug items]*
Taiwan Intellectual Property Office. (n.d.). *Global Patent Search System (GPSS)*
US Food and Drug Administration. (n.d.–b). *Search Orphan Drug Designations and Approvals*

Report

Aitken, M., Kleinrock, M., Campanelli, G., Tawil, C., & Vokey, M. (2020). *Medicine Spending and Affordability in the United States*.
Aitken, M., Pritchett, J., & Jaishankar, A. (2024). *Strengthening Pathways for Cell and Gene Therapies*. https://www.iqvia.com/-/media/iqvia/pdfs/institute-

doi:10.6342/NTU202502665

reports/strengthening-pathways-for-cell-and-gene-therapies/iqvia-institute-cagt-report-03-24-forweb.pdf
Alliance for Regenerative Medicine. (2023a). *Innovative Contracting for ATMPs in Europe*. Alliance for Regenerative Medicine. https://alliancerm.org/innovative-contracting-for-atmps-in-europe/
Alliance for Regenerative Medicine. (2023b). *Issue Brief: Medicaid Barriers to Accessing Cell & Gene Therapies*. Alliance for Regenerative Medicine. https://alliancerm.org/medicaid-barriers-to-accessing-cell-gene-therapies/
Alliance for Regenerative Medicine. (n.d.). *Joint Clinical Assessment for Advanced Therapy Medicinal Products*. Alliance for Regenerative Medicine. https://alliancerm.org/indication-data/joint-clinical-assessment-for-advanced-therapy-medicinal-products/
American Society of Gene and Cell Therapy, & CITELINE. (n.d.). *Gene, Cell, & RNA Therapy Landscape Report-Q4 2024 Quarterly Data Report*.
Ernst, D. (1997). *From Partial to Systemic Globalization- International Production Networks in the Electronics Industry* (BRIE Working Paper, Issue.
Liu, J. P. (2024). *Zài shēng yī liáo zhì jì tiáo lì jí guó jì hé zhǔn xiàn kuàng [Regenerative Medicine Product Act and International Approval Status]*. https://www.twpharmconf.org.tw/upload/program/20241218/492d413fea434a52bc93629e56ff53c9/492d413fea434a52bc93629e56ff53c9.pdf
Ministry of Health and Welfare. (2025a). *2024 Annual Report of Cell Therapy*. https://celltherapy.mohw.gov.tw/announcement_page.htm?id=128
Office of the Assistant Secretary for Planning and Evaluation. (2025). *Health Insurance Coverage and Healthcare Access from 2021-2024*. https://aspe.hhs.gov/reports/healthcare-coverage-access-2021-2024
Phares, S., Trusheim, M., Emond, S. K., & Pearson, S. D. (2024). *Managing the Challenges of Paying for Gene Therapy: Strategies for Market Action and Policy Reform*. Institute for Clinical and Economic Review.
Precedence Research. (n.d.). *Cell and Gene Therapy Market Size | Share and Trends 2025 to 2034*. https://www.precedenceresearch.com/cell-and-gene-therapy-market
The Royal Swedish Academy of Sciences. (2020). *Genetic scissors: a tool for rewriting the code of life*. https://www.nobelprize.org/uploads/2020/10/popular-chemistryprize2020.pdf
US Census Bureau. (2024). *Health Insurance Coverage in the United States: 2023* (Current Population Reports, Issue. U.S. Government Publishing Office. https://www2.census.gov/library/publications/2024/demo/p60-284.pdf

Unpublished Work

Maruyama, Y. (2024). *Regulatory Update of Regenerative Medicine in Japan* [Presentation]. Ministry of Health Labour and Welfare, Japan,. https://www.pmda.go.jp/files/000269742.pdf

Web Page

Adaptimmune. (March 6, 2023). *Adaptimmune and TCR2 Therapeutics Announce Strategic Combination to Create a Preeminent Cell Therapy Company for Solid Tumors*. Adaptimmune. Retrieved June 10 from https://www.adaptimmune.com/investors-and-media/news-center/press-releases/detail/241/adaptimmune-and-tcr2-therapeutics-announce-strategic
Amarin. (n.d.). *Official Website of Amarin*. Retrieved June 13 from

doi:10.6342/NTU202502665

https://www.amarincorp.com/
American Society of Gene and Cell Therapy. (n.d.). *Gene Therapy Approaches*. American Society of Gene and Cell Therapy. Retrieved May 30 from https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-approaches
Chen, J. (April 25, 2023). *Zì fèi xì bāo liáo fǎ Tái dà, Róng zǒng wèi hé fǎn yìng lěng? Zhì liáo jiū fēn nán rèn dìng, yī bìng bǎo zhàng jiē bù zú [Why are NTU and Veterans General Hospital so cold about self-funded cell therapy? Treatment disputes are difficult to identify, and medical and disease insurance is insufficient]*. The Reporter. Retrieved July 8 from https://www.twreporter.org/a/regenerative-medicine-patients-rights
Children's Hospital of Philadelphia. (2022). *Emily Whitehead, First Pediatric Patient to Receive CAR T-Cell Therapy, Celebrates Cure 10 Years Later*. Children's Hospital of Philadelphia. Retrieved April 6 from https://www.chop.edu/news/emily-whitehead-first-pediatric-patient-receive-car-t-cell-therapy-celebrates-cure-10-years
CITELINE. (January 21, 2025). *The World's Top 100 Pharma Companies: 2024 Sales Rankings*. Citeline. Retrieved June 17 from https://insights.citeline.com/pharma-insights/the-worlds-top-100-pharma-companies-2024-sales-rankings-Z47XBTXVNJEXFCKYU7Q4EJ45XI/
Dennis, M. (May 26, 2022). *J&J, Legend's CAR-T therapy Carvykti cleared in Europe*. FirstWorld PHARMA. Retrieved June 26 from https://firstwordpharma.com/story/5580359
editorv. (May 9, 2024). *1120511Qiǎn zé zài shēng yī liáo fǎ cū bào xié shāng, kǒng xī shēng yī bìng quán lì [1120511 Condemning the rough negotiation of the Regenerative Medicine Act, which may sacrifice the rights of patients]*. Taiwan Healthcare Reform Foundation. Retrieved July 3 from https://www.thrf.org.tw/initiative/2428
editorv. (May 9, 2024). *Zàishēng yīliáo fǎ chǎo shénme? Tīng gèlù zhuānjiā zhèngyán! [What's the fuss about the Regenerative Medicine Act? Here are the experts' opinions!]*. Taiwan Healthcare Reform Foundation. Retrieved July 3 from https://www.thrf.org.tw/initiative/2430
Emily Whitehead Foundation. (n.d.). *Our Journey*. Emily Whitehead Foundation. Retrieved April 6 from https://emilywhiteheadfoundation.org/our-journey/
European Commission. (June 10, 2025). *Implementation of the Regulation on health technology assessment*. European Commission. Retrieved June 22 from https://health.ec.europa.eu/health-technology-assessment/implementation-regulation-health-technology-assessment_en
Foundation, N. B. D. (n.d.). *Hemophilia B*. National Bleeding Disorders Foundation. Retrieved July 27 from https://www.bleeding.org/bleeding-disorders-a-z/types/hemophilia-b
Huang, H. M. (June 4, 2024). *lì jīng 10nián ，zài shēng yī liáo shuāng fǎ sān dú ！shì yòng duì xiàng 、xì bāo shǐ yòng 、lún lǐ guī fàn ，6dà jiāo diǎn yī cì kàn [After 10 years, the two laws on regenerative medicine have been read three times! Applicable subjects, cell use, ethical standards, 6 major focuses at a glance]*. The Reporter. Retrieved May 30 from https://www.twreporter.org/a/regenerative-medicine-legislation-passed
Inserm. (May 9, 2025). *Inserm at a Glance*. Retrieved June 13 from https://www.inserm.fr/en/about-us/inserm-at-a-glance/
Keown, A. (August 7, 2019). *More M&A Activity Expected Around AAV-Based Gene Therapies, Analyst Says*. BioSpace. Retrieved July 27 from

doi:10.6342/NTU202502665

https://www.biospace.com/more-m-and-a-activity-expected-around-aav-based-gene-therapies-analyst-says
Kou, Y. H. (March 14, 2025). *jī yīn zhì liáo chǎn pǐn fā zhǎn xiàn kuàng yǔ qū shì[Current Status and Trends of Gene Therapy Product Development]*. Development Center for Biotechnology. Retrieved May 30 from https://www.dcb.org.tw/posts/1092?locale=zh-TW
Lai, S. M., & Jiang, L. X. (June 4, 2024). *Zài shēng yī liáo shuāng fǎ sān dú, yī jì yǔ xì bāo yuán tóu huò fǎ yuán [The third reading of the two acts on regenerative medicine: medical technology and cell sources gain legal basis]*. PTS News. Retrieved July 3 from https://news.pts.org.tw/article/698484
Lin, C.-Y. (November 2, 2023). *CAR-T liè jiàn bǎo zàn shí xìng zhī fù 7 yuàn suǒ kě tí gòng zhì liáo [CAR-T is temporarily covered by the National Health Insurance, and 7 hospitals can provide treatment]*. Yahoo! News. Retrieved May 31 from https://tw.news.yahoo.com/car-t%E5%88%97%E5%81%A5%E4%BF%9D%E6%9A%AB%E6%99%82%E6%80%A7%E6%94%AF%E4%BB%98-7%E9%99%A2%E6%89%80%E5%8F%AF%E6%8F%90%E4%BE%9B%E6%B2%BB%E7%99%82-042244531.html
Liu, X. T. (January 7, 2020). *Bǎi wàn yuán huā fèi pǎo bù diào! Yī cì gǎo dǒng ái zhèng xì bāo liáo fǎ sān duàn shōu fèi [No escaping the million-dollar bill! A quick guide to the three-stage pricing of cancer cell therapy.]*. Wealth Magazine. Retrieved June 25 from https://www.wealth.com.tw/articles/3887cf95-8861-401e-ae3f-97d6f13cfef2
Liu, X. T., & Hung, L. X. (August 19, 2024). *zài shēng yī liáo xīn gé mìng 5》yī cì kàn dǒng ，zài shēng yī liáo guān jiàn 5wèn liáo xiào 、jià gé 、bǎo xiǎn gè yǒu méi jiǎo [A New Revolution in Regenerative Medicine 5: Understand the 5 key questions about regenerative medicine at once: efficacy, price, and insurance, each with its own unique characteristics]*. Wealth Magazine. Retrieved May 30 from https://www.wealth.com.tw/articles/e070e3eb-768e-4c95-91b6-56f35b22e29d
MS Technologies. (n.d.). *Official Website*. MS Technologies. Retrieved Jun 15 from https://www.mstechseed.com/
Ng, D. (July 24, 2024). *A Brief History of CRISPR-Cas9 Genome-Editing Tools*. BiteSize Bio. Retrieved April 8 from https://bitesizebio.com/47927/history-crispr/
Pagliarulo, N. (October 21, 2021). *Bluebird, winding down in Europe, withdraws another rare disease gene therapy*. BIOPHARMA DIVE. Retrieved July 7 from https://www.biopharmadive.com/news/bluebird-withdraw-gene-therapy-europe-skysona/608666/
Pagliarulo, N. (February 21, 2025). *Pfizer stops selling hemophilia gene therapy, citing weak demand*. Retrieved March 24 from https://www.biopharmadive.com/news/pfizer-beqvez-hemophilia-halt-sales-gene-therapy/740590/
Pategou, J. (January 28, 2025). *Catalysts of Change: How the Cell and Gene Therapy Market Has Evolved*. Cell and Gene. Retrieved April 6 from https://www.cellandgene.com/doc/catalysts-of-change-how-the-cell-and-gene-therapy-market-has-evolved-0001
Peng, Z.-H. (August 14, 2024). *Xiān jìn yào pǐn jǐ fù luò dì nán? Zhuān jiā jiě xī Tái wān yǔ gè guó nà bǎo cè lüè, shǒu zhōng HTA, RWE [Challenges in Reimbursement of Advanced Therapies? Experts Analyze Taiwan and International Coverage Strategies, Focusing on HTA and RWE]*. Global Bio. Retrieved May 31 from

doi:10.6342/NTU202502665

https://news.gbimonthly.com/tw/article/show.php?num=70452
Peter, R. M. (May 12, 2025). *Pharma giants pull back on AAV research: what's next for the gene therapy space?* LABIOTECH. Retrieved July 27 from https://www.labiotech.eu/trends-news/aav-gene-therapy-pharma-pullback/
Rudowitz, R., Tolbert, J., Burns, A., Hinton, E., & Mudumala, A. *Medicaid 101*. KFF. https://www.kff.org/health-policy-101-medicaid/?entry=table-of-contents-citation
Sandra Johannesson, M. (April 29, 2024). *Advanced Therapy Medicinal Product (ATMP) Regulations in Europe – 2024 Report*. CAR T-Cell Advisory by Medrego. Retrieved March 18 from https://cartcell.medrego.com/advanced-therapy-medicinal-product-atmp-regulations-in-europe-2024-report/
Smith, D. (May 6, 2025). *Gene Therapy at a Crossroads: Rethinking AAV Amid Industry Resets*. pharma's almanac. Retrieved July 27 from https://www.pharmasalmanac.com/articles/gene-therapy-at-a-crossroads-rethinking-aav-amid-industry-resets
Smith, G. (September 9, 2024). *Cures for rare diseases now exist: Employers don't want to pay*. Retrieved March 24 from https://medicalxpress.com/news/2024-09-rare-diseases-employers-dont-pay.html?utm_source=chatgpt.com#google_vignette
Vandermosten, J. (March 18, 2020). *Gene Therapy M&A: Best Prospects 2020*. American Gene Technologies. Retrieved July 27 from https://www.americangene.com/blog/gene-therapy-ma-best-prospects-2020/
Warner, E. (April 20, 2017). *Goodbye Glybera! The World's First Gene Therapy will be Withdrawn*. LABIOTECH. Retrieved June 30 from https://www.labiotech.eu/trends-news/uniqure-glybera-marketing-withdrawn/
Wu, O. (25 February, 2025). *Wèi fú bù zài shēng yī liáo liù xiàng zǐ fǎ guī: ná nīe tuī xíng yǔ pǐn zhí lún lǐ jiān de píng héng diǎn [Taiwan's Six Sub-Regulations on Regenerative Medicine: Balancing Policy Implementation with Ethical and Quality Standards]*. Gene Online. Retrieved May 30 from https://geneonline.news/six-sub-regulations-on-regenerative-medicine-from-mohw-find-the-balance-between-implementation-and-quality-ethics/
Wu, P. A. (April 22, 2024). *Guó xǐ xì bāo xīn yào + CDMO shuāng guǐ cè lüè, dàn zài shēng yīl iáo shuāng fǎ shāng jī [Gwoxi's dual-track strategy of new cell medicine + CDMO captures dual business opportunities in regenerative medicine]*. Global Bio & Investment. Retrieved July 3 from https://news.gbimonthly.com/tw/article/show.php?num=76268&range=news
Xì bāo zhìl iáo fèi yòng gāo zěn me bàn? Jiě xī zài shēng yī xué jiàn bǎo jǐ fù yǔ shāng yè bǎo xiǎn bǔ zhù fāng 'àn [What can be done about the high cost of cell therapy? Analyzing reimbursement through national health insurance and commercial insurance support in regenerative medicine]. (June 16, 2025). We Get Care. Retrieved July 27 from https://www.wegetcare.tw/post/cell-therapy-cost-insurance-taiwan?srsltid=AfmBOoq97qRjsD_8h0moPjiLmdYLQ5OzAwsDR3B5k7ySz-REhLAy3_F4#viewer-uk07f1839
Yang, X. Y., & Lin, Y. H. (March 29, 2023). *[Tóu shū] Kāi cè mén de zài shēng yī liáo fǎ, mín zhòng néng xìn lài ma? [[Letter] Can the public trust the side-door regenerative medicine method?]*. CommonWealth Magazine. Retrieved July 3 from https://opinion.cw.com.tw/blog/profile/52/article/13444
You, Y. T. (June 5, 2024). *Zài shēng yī liáo fǎ sān dú tōng guò! Zài shēng yī liáo fǎ shì shén me? Guò qù zhēng yì, wèi lái yǐng xiǎng fēn xī [The Regenerative Medicine Act passed the third reading! What is the Regenerative Medicine Act? Analysis of*

doi:10.6342/NTU202502665

past controversies and future impacts]. Business Weekly. Retrieved July 3 from https://www.businessweekly.com.tw/focus/blog/3015793

Zhou, J. H., & Lin, Y. K. (October 31, 2022). *Shēngyīchǎn yètòu guòshòu quánbìng gòujíhé zīdǎ zàoxiàyī zuò [The biomedical industry is building the next national guardian mountain through licensing, mergers and acquisitions, and joint ventures]*. PwC. Retrieved May 31 from https://www.pwc.tw/zh/news/press-release/press-20221031-1.html

Patent

Amusan, I. (2019). *Inbred corn line KM5* (United States Patent No. US10165744B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Asoro, F. G., Bhatnagar, S., Eller, M. S., Eller, R. C., Gehlhar, S., Lubich, D. J., McElroy, J. L., Potrzeba, D. A., & Reeder, L. R. (2018). *Plants and seeds of hybrid corn variety CH624975* (United States Patent No. US10070611B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Bachmann, M., & Ehninger, A. (2020). *Universal chimeric antigen expressing immune cells for targeting of diverse multiple antigens and method of manufacturing the same and use of the same for treatment of cancer, infections and autoimmune disorders* (United States Patent No. US10611814B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Baeuerle, P., Sieczkiewicz, G., & Hofmeister, R. (2019). *Compositions and methods for TCR reprogramming using fusion proteins* (United States Patent No. US10442849B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Baeuerle, P., Sieczkiewicz, G., & Hofmeister, R. (2021). *Compositions and methods for TCR reprogramming using fusion proteins* (United States Patent No. US11028142B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Baeuerle, P., Sieczkiewicz, G., & Hofmeister, R. (2024). *Compositions and methods for TCR reprogramming using fusion proteins* (United States Patent No. US11965012B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Barker, T. C., Cabral, C. B., Weber, G. P., & Yu, J. (2019). *Maize hybrid X95M194* (United States Patent No. US10219471B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Barrangou, R., Boyaval, P., Fremaux, C., & Romero, P. H. (2018). *Method of modulating cell resistance* (United States Patent No. US10066233B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Barrangou, R., & Briner, K. M. S. E. (2020). *Methods and compositions for sequence guiding Cas9 targeting* (United States Patent No. US10787654B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Belgrader, P., Bent, Z., Gopalan, V. K. S., Harada, J., Hindson, C., Lenji, M. R., McDermott, G., Meer, E., Mikkelsen, T. S., O'Keeffe, C. J., Pfeiffer, K., Price, A. D., Ryvkin, P., Saxonov, S., Stuelpnagel, J. R., & Terry, J. M. (2018). *Methods and systems for processing polynucleotides* (United States Patent No. US10011872B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Benson, M., Merkin, J., Kryukov, G. V., Shenker, S. M., Schlabach, M., & Tubo, N. (2021). *Gene-regulating compositions and methods for improved immunotherapy*

doi:10.6342/NTU202502665

(United States Patent No. US11111493B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Bernett, M., Rashid, R., Desjarlais, J., Varma, R., & Bonzon, C. (2020). *Bispecific heterodimeric fusion proteins containing IL-15-IL-15Rα Fc-fusion proteins and PD-1 antibody fragments* (United States Patent No. US10550185B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Bhatnagar, S., Chen, Y., Gutierrez, H. I., Nichols, D. M., & Tiwari, K. R. (2022). *Plants and seeds of hybrid corn variety CH011149* (United States Patent No. US11388874B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Bhatnagar, S., Nichols, D. M., & Tiwari, K. R. (2024). *Plants and seeds of hybrid corn variety CH011015* (United States Patent No. US12058974B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Brogdon, J., Choi, E., Ebersbach, H. E., Glass, D., Huet, H., June, C. H., Mannick, J., Milone, M. C., Murphy, L., Plesa, G., Richardson, C., Ruella, M., Singh, R., Wang, Y., & Wu, Q. (2019). *Nucleic acid encoding a humanized anti-BCMA chimeric antigen receptor* (United States Patent No. US10174095B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Buffard, C. J., Sernett, J. M., & Stangland, G. R. (2019). *Plants and seeds of hybrid corn variety CH482861* (United States Patent No. US10362756B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Buffard, C. J., Sernett, J. M., & Stangland, G. R. (2023). *Plants and seeds of hybrid corn variety CH011102* (United States Patent No. US11606924B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Campana, D., Shook, D., & Imamura, M. (2019). *Modified natural killer cells that express IL15 and uses thereof* (United States Patent No. US10428305B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Carton, J. M., Naso, M. F., Borges, L. G., Wheeler, J., & Devaney, A. (2024). *Chimeric antigen receptor system with adaptable receptor specificity* (United States Patent No. US11883432B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Chand, D. S., Jawad, Z., Ignatovich, O., Ramsay, N. A., Campbell, S., Wensley, B., Briend, E. C. P., Bushell, K. M., Morin, B. M., & Ilkow, V. F. (2022). *Anti-TIGIT and anti-CD96 antibodies* (United States Patent No. US11718669B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Chand, D. S., Wilson, N. S., Underwood, D. J., & Morin, B. M. (2021). *Anti-TIGIT antibodies and methods of use thereof* (United States Patent No. US11021537B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Chee, M. S., Gong, H., & Gunderson, K. L. (2023). *Methods for barcoding macromolecules in individual cells* (United States Patent No. US11753677B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Cheung, N.-K. V., Lopez-Albaitero, A., & Xu, H. (2019). *Bispecific HER2 and CD3 binding molecules* (United States Patent No. US10519248B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Chopin, F., Page, N. J., & Roucolle, J. (2019). *Plants and seeds of hybrid corn variety CH267399* (United States Patent No. US10362754B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Chung, S. (2023). *Methods for efficient generation of GABAergic interneurons from pluripotent stem cells* (United States Patent No. US11767507B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

doi:10.6342/NTU202502665

Ciaramella, G., & Himansu, S. (2018). *Combination PIV3/hMPV RNA vaccines* (United States Patent No. US10064934B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Ciaramella, G., & Himansu, S. (2020). *Betacoronavirus mRNA vaccine* (United States Patent No. US10702600B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Ciaramella, G., Huang, E. Y.-C., Bahl, K., Zaks, T., & Himansu, S. (2018). *Zika RNA vaccines* (United States Patent No. US10449244B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Clube, J. (2019). *Altering microbial populations and modifying microbiota* (United States Patent No. US10506812B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Clube, J. (2021). *Selectively altering microbiota for immune modulation* (United States Patent No. US11141481B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Clube, J. (2022). *Selectively altering microbiota for immune modulation* (United States Patent No. US11351252B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Clube, J., Sommer, M., Grøndahl, C., HELM, E. V. D., & VAZQUEZ-URIBE, R. (2023). *Altering microbial populations and modifying microbiota* (United States Patent No. US11844760B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Cogswell, J. P., Goldberg, S. M., Gupta, A. K., Jure-Kunkel, M., Wang, X.-T., & Wigginton, J. M. (2018). *Cancer immunotherapy by disrupting PD-1/PD-L1 signaling* (United States Patent No. US10072082B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Conway, A., Cost, G. J., Dekelver, R., Rebar, E. J., Reik, A., Urnov, F., Wang, J., & Zhang, H. S. (2019). *Methods and compositions for treatment of a genetic condition* (United States Patent No. US10196651B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Cooper, L. J. N., KORNGOLD, A. B., RABINOVICH, B. A., Singh, H., & OLIVARES, S. (2018). *Chimeric antigen receptors and methods of making* (United States Patent No. US10125193B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Cotta-Ramusino, C., & Margulies, C. M. (2024). *Systems and methods for targeted integration and genome editing and detection thereof using integrated priming sites* (United States Patent No. US11866726B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Crowley, N. A., Cunnyngham, C. T., Gadlage, M. J., Henry, T. R., Holley, R. N., Lennon, J. R., O'Berry, N. B., Pohl, D. J., & Steinke, J. A. (2022). *Maize hybrid X13N234* (United States Patent No. US11490584B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Crowley, N. A., Cunnyngham, C. T., Henry, T. R., Holley, R. N., Lennon, J. R., Steinke, J. A., & Thurston, A. K. (2022). *Maize hybrid X15P092* (United States Patent No. US11528874B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Deisseroth, K. A., Allen, W. E., HSUEH, B., & Ye, L. (2019). *Method and system for imaging and analysis of a biological specimen* (United States Patent No. US10495554B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

doi:10.6342/NTU202502665

Denham, G. J., & Stone, K. T. (2018). *Method and apparatus for coupling soft tissue to a bone* (United States Patent No. US10092288B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Denham, G. J., & Stone, K. T. (2020). *Method and apparatus for coupling soft tissue to a bone* (United States Patent No. US10729430B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Dequeant, M.-L., Kalaitzidis, D., & Ghonime, M. (2022). *Genetically engineered t cells with regnase-1 and/or TGFBRII disruption have improved functionality and persistence* (United States Patent No. US11497773B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Desjarlais, J. R., Moore, G., Hedvat, M., Diaz, J., & Zeng, V. G. (2024). *Anti-CD28 compositions* (United States Patent No. US11919958B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Dever, D. P., Bak, R. O., Hendel, A., Srifa, W., & Porteus, M. H. (2021). *Nuclease-mediated genome editing of primary cells and enrichment thereof* (United States Patent No. US11193141B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Dever, D. P., Bak, R. O., Hendel, A., Srifa, W., & Porteus, M. H. (2022). *Nuclease-mediated genome editing of primary cells* (United States Patent No. US11492646B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Dever, D. P., Bak, R. O., Hendel, A., Srifa, W., & Porteus, M. H. (2023). *Pharmaceutical compositions comprising gene-corrected primary cells* (United States Patent No. US11634732B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M. (2018). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10085843B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M. (2019). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10492918B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M., & Malone, J. D. (2019). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10433971B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M., & Slivka, M. A. (2020a). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10555817B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M., & Slivka, M. A. (2020). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10575959B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M., & Slivka, M. A. (2020). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10583013B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DiMauro, T. M., & Slivka, M. A. (2020b). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10639164B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Doudna, J. A., Al-Shayeb, B., Banfield, J. F., & Pausch, P. (2023a). *CRISPR-Cas12J effector polypeptides and methods of use thereof* (United States Patent No. US11739309B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

doi:10.6342/NTU202502665

Doudna, J. A., Al-Shayeb, B., Banfield, J. F., & Pausch, P. (2023b). *CRISPR-Cas effector polypeptides and methods of use thereof* (United States Patent No. US11578313B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DOUDNA, J. A., Banfield, J., Burstein, D., Harrington, L. B., & Strutt, S. C. (2020). *RNA-guided nucleic acid modifying enzymes and methods of use thereof* (United States Patent No. US10570415B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Doudna, J. A., Banfield, J., Burstein, D., Harrington, L. B., & Strutt, S. C. (2023). *RNA-guided nucleic acid modifying enzymes and methods of use thereof* (United States Patent No. US11795472B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DOUDNA, J. A., Banfield, J. F., Burstein, D., Harrington, L. B., & Strutt, S. C. (2024). *RNA-guided nucleic acid modifying enzymes and methods of use thereof* (United States Patent No. US11873504B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

DOUDNA, J. A., Chen, J. S., Harrington, L. B., & Ma, E. (2019). *Type V CRISPR/Cas effector proteins for cleaving ssDNAs and detecting target DNAs* (United States Patent No. US10253365B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Doudna, J. A., Chen, J. S., Harrington, L. B., & Ma, E. (2021). *Type V CRISPR/Cas effector proteins for cleaving ssDNAs and detecting target DNAs* (United States Patent No. US11118224B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Doudna, J. A., Lin, S., & Staahl, B. T. (2020). *Methods and compositions for RNA-directed target DNA modification* (United States Patent No. US10570418B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Dupont, J., & Parmar, H. (2021). *Methods for treatment of cancer comprising TIGIT-binding agents* (United States Patent No. US11136384B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Dupont, J., & Parmar, H. (2022). *Methods for treatment of cancer comprising TIGIT-binding agents* (United States Patent No. US11230596B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Eisenbach-Schwartz, M., Baruch, K., & Rosenzweig, N. (2018). *Reducing systemic regulatory T cell levels or activity for treatment of disease and injury of the CNS* (United States Patent No. US10144778B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Faham, M., & Willis, T. (2019). *Methods of monitoring conditions by sequence analysis* (United States Patent No. US10246752B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Fang, L., Wang, Z., Guo, B., & Zang, J. (2019). *Anti-PD-L1 antibodies and uses thereof* (United States Patent No. US10208119B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Feng, Q., Lu, S.-J., & Lanza, R. P. (2019). *Methods for production of platelets from pluripotent stem cells and compositions thereof* (United States Patent No. US10426799B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Feng, Q., Lu, S.-J., & Lanza, R. P. (2021). *Methods for production of platelets from pluripotent stem cells and compositions thereof* (United States Patent No. US10894065B2). United States Patent and Trademark Office.

doi:10.6342/NTU202502665

https://tiponet.tipo.gov.tw/gpss/
Ferrara Koller, C., Junttila, T. T., Klein, C., Umana, P., & Claus, C. (2024). *HER2-targeting antigen binding molecules comprising 4-1BBL* (United States Patent No. US12065478B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Fox, R., Heffner, E. L., Henke, G. E., Lira, S. J., Srnic, G., & Tarnowski, T. L. B. (2021). *Maize hybrid X13N261* (United States Patent No. US10905063B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Frisen, J., Stahl, P., Lundeberg, J., Cann, G. M., Bazargan, L., & Aravanis, A. (2023a). *Spatially distinguished, multiplex nucleic acid analysis of biological specimens* US11613773B2). https://patents.google.com/patent/US11613773B2/en?oq=US11613773B2
Frisen, J., Stahl, P., Lundeberg, J., Cann, G. M., Bazargan, L., & Aravanis, A. (2023b). *Spatially distinguished, multiplex nucleic acid analysis of biological specimens* (United States Patent No. US11613773B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Fritsche, J., Weinschenk, T., Walter, S., Lewandrowski, P., & Singh, H. (2021). *Immunotherapy against several tumors including gastrointestinal and gastric cancer* (United States Patent No. US11077171B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
FRITSCHE, J., Weinschenk, T., Walter, S., LEWANDROWSKI, P., & Singh, H. (2022a). *Immunotherapy against several tumors including gastrointestinal and gastric cancer* (United States Patent No. US11298404B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
FRITSCHE, J., Weinschenk, T., Walter, S., LEWANDROWSKI, P., & Singh, H. (2022b). *Immunotherapy against several tumors including gastrointestinal and gastric cancer.* (United States Patent No. US11273200B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Fritsche, J., Weinschenk, T., Walter, S., Lewandrowski, P., & Singh, H. (2023). *Immunotherapy against several tumors including gastrointestinal and gastric cancer* (United States Patent No. US11839643B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Gill, R. T., Garst, A., & LIPSCOMB, T. E. W. (2018). *Nucleic acid-guided nucleases* (United States Patent No. US10011849B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Grandal, M. M., Gjetting, T., Lantto, J., Jakobsen, J. S., HANSEN, R. W., & Fröhlich, C. (2023). *Anti-CD73 antibodies and compositions* (United States Patent No. US11634500B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Gurney, A. L., & Xie, M.-H. (2018). *Tight-binding agents and uses thereof* (United States Patent No. US10112997B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
HAABER, J. K., SEMSEY, S., Grove, M., DAMHOLT, B., Jasinskyte, D., & Gençay, Y. E. (2024). *Treating and preventing E coli infections* (United States Patent No. US12076375B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Hawkins, J. R., Upal, A. M., O'Neil, M. J., Slivka, M. A., & Fisher, M. (2021). *Highly lordosed fusion cage* (United States Patent No. US10973652B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Higginson-Scott, N., Viney, J. L., Otipoby, K. L., Visweswaraiah, J., Alioto, S., Edwards,

doi:10.6342/NTU202502665

L. J., Sampson, E., Glanville, J., Maurer, D., Ives, S., Pettus, C., & Schwimmer, L. (2023). *MAdCAM targeted immunotolerance* (United States Patent No. US11739146B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Hindson, B., Hindson, C., Schnall-Levin, M., Ness, K., Jarosz, M., Saxonov, S., & Hardenbol, P. (2019). *Methods and systems for processing polynucleotides* (United States Patent No. US10273541B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Holley, R. N. (2020). *Maize inbred PH46C2* (United States Patent No. US10716278B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Huang, Y.-C., Ivery, A., Choi, B., Schilling, B., & Ngo, M.-D. (2018). *Method of preparing an adipose tissue derived matrix* (United States Patent No. US10092600B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Huntington, N. D., Nicholson, S. E., Babon, J., & Kolesnik, T. (2021). *Inhibition of cytokine-induced SH2 protein in NK cells* (United States Patent No. US10975149B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Jacques, Y., Plet, A., Mortier, E., Quemener, A., & Vusio, P. (2019). *IL-15Ralpha sushi domain—IL-15 fusion proteins* (United States Patent No. US10358477B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Jaenisch, R., Hanna, Y., Wernig, M., Lengner, C. J., Meissner, A., Brambrink, O. T., Welstead, G. G., & Foreman, R. (2018). *Reprogramming of somatic cells* (United States Patent No. US10093904B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Jaenisch, R., & Hochedlinger, K. (2019). *Methods for reprogramming somatic cells* (United States Patent No. US10457917B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

JASNY, E., & Petsch, B. (2024). *Lassa virus vaccine* (United States Patent No. US12161711B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Jensen, M. (2019). *Bispecific chimeric antigen receptors and methods of use thereof to treat cancer* (United States Patent No. US10189903B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Jensen, M. C. (2022). *Bispecific CAR T-cells for solid tumor targeting* (United States Patent No. US11458167B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Kahvejian, A., Mata-Fink, J., Deans, R. J., Chen, T. F., Round, J., Afeyan, N. B., Nissen, T. S., Dowden, N., Wickham, T., & Elloul, S. (2019). *Compositions and methods related to engineered erythoid cells comprising 4-1BBL* (United States Patent No. US10456421B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Kahvejian, A., Mata-Fink, J., Round, J., Berry, D. A., & Afeyan, N. B. (2019). *Synthetic membrane-receiver complexes* (United States Patent No. US10329531B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Kannan, K., Gander, M., Spindler, E., & Hardenbol, P. (2021). *Increased nucleic-acid guided cell editing in yeast* (United States Patent No. US10927385B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Kariko, K., & Weissman, D. (2019). *RNA containing modified nucleosides and methods of use thereof* (United States Patent No. US10232055B2). United States Patent

doi:10.6342/NTU202502665

and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Kelly, J. E., & DiMauro, T. M. (2019). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10405986B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Klemke, R., & Wang, H. (2022). *Platform for generating safe cell therapeutics* (United States Patent No. US11248213B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Klemke, R., & Wang, H. (2023). *Platform for generating safe cell therapeutics* (United States Patent No. US11674121B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Klemke, R., & Wang, H. (2024). *Platform for generating safe cell therapeutics* (United States Patent No. US12049644B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Klimanskaya, I., Carson, J. K., Gay, R., & Ivanova, Y. G. (2023). *Assays for potency of human retinal pigment epithelium (RPE) cells and photoreceptor progenitors* (United States Patent No. US11680941B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Klimanskaya, I. V., Carson, J. K., Gay, R., & Ivanova, Y. G. (2022). *Assays for potency of human retinal pigment epithelium (RPE) cells and photoreceptor progenitors* (United States Patent No. US11422125B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Kochenderfer, J. N. (2023). *Chimeric antigen receptors targeting B-cell maturation antigen* (United States Patent No. US11827889B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Lanza, R. P., Lu, S.-J., & Wang, W. (2019). *Photoreceptors and photoreceptor progenitors produced from pluripotent stem cells* (United States Patent No. US10307444B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Lee, G. K., Riley, B. E., St. Martin, S. J., & Wechsler, T. (2019). *Delivery methods and compositions for nuclease-mediated genome engineering* (United States Patent No. US10450585B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Lonberg, N., Korman, A. J., Barnhart, B. C., Yamniuk, A. P., Srinivasan, M., Henning, K. A., Lei, M., Sega, E., Goodenough, A., Jure-Kunkel, M., Chen, G., Sack, J. S., HUANG, R. Y., Corbett, M. J., Joseph E. Myers, J., Schweizer, L., Hatcher, S. V., Huang, H., & Zhang, P. (2018). *Antibodies against CD73 and uses thereof* (United States Patent No. US10100129B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Lubich, D. J., & Nichols, D. M. (2022). *Plants and seeds of hybrid corn variety CH011133* (United States Patent No. US11464188B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Maglaras, C., & Valdevit, A. (2020). *Load sustaining bone scaffolds for spinal fusion utilizing hyperbolic struts and translational strength gradients* (United States Patent No. US10660764B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Mahr, A., Weinschenk, T., Goldfinger, V., Schoor, O., Fritsche, J., & Singh, H. (2021). *Peptides and combination of peptides for use in immunotherapy against small cell lung cancer and other cancers* (United States Patent No. US11111280B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
MAHR, A., Weinschenk, T., HOERZER, H., Schoor, O., FRITSCHE, J., & Singh, H. (2024a). *Peptides and combination of peptides for use in immunotherapy against*

doi:10.6342/NTU202502665

ovarian cancer and other cancers (United States Patent No. US12071458B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

MAHR, A., Weinschenk, T., HOERZER, H., Schoor, O., FRITSCHE, J., & Singh, H. (2024b). *Peptides and combination of peptides for use in immunotherapy against ovarian cancer and other cancers* (United States Patent No. US11912749B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

MAHR, A., Weinschenk, T., HOERZER, H., Schoor, O., FRITSCHE, J., & Singh, H. (2024c). *Peptides and combination of peptides for use in immunotherapy against ovarian cancer and other cancers* (United States Patent No. US11912748B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Malcuit, C., Lemieux, L., Holmes, W., Huertas, P., & Vilner, L. (2019). *Methods of producing human RPE cells and pharmaceutical preparations of human RPE cells* (United States Patent No. US10485829B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Manku, M., Osterloh, I., Wicker, P., Braeckman, R., Soni, P., & Zakrzewski, J. S. (2019a). *Methods of reducing apolipoprotein C-III* (United States Patent No. US10265290B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Manku, M., Osterloh, I., Wicker, P., Braeckman, R., Soni, P., & Zakrzewski, J. S. (2019b). *Methods of reducing apolipoprotein C-III* (United States Patent No. US10166209B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mason, J. T. (2019). *Soybean cultivar S170170* (United States Patent No. US10470423B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mason, J. T. (2021a). *Soybean cultivar 84410120* (United States Patent No. US11006605B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mason, J. T. (2021b). *Soybean cultivar 95130648* (United States Patent No. US11178840B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mason, J. T. (2022a). *Soybean cultivar 90442929* (United States Patent No. US11337397B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mason, J. T. (2022b). *Soybean cultivar 92312145* (United States Patent No. US11337396B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mata-Fink, J., Round, J., Afeyan, N. B., & Kahvejian, A. (2020). *Methods and compositions for immunomodulation* (United States Patent No. US10869898B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Maurer, M. F., Chen, T.-h. T., Devaux, B., Srinivasan, M., Julien, S. H., Sheppard, P. O., Ardourel, D. F., & Chakraborty, I. (2019). *Antibodies to TIGIT* (United States Patent No. US10189902B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

McAllister, M., Wang, D., Bubear, M., Canales, J., Chang, A., Shikhanovich, R., Spilker, M., & Semler, E. (2020). *Modified demineralized cortical bone fibers* (United States Patent No. US10531957B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

McAllister, M., Wang, D., Bubear, M., Canales, J., Chang, A., Shikhanovich, R., Spilker, M., & Semler, E. (2023). *Modified demineralized cortical bone fibers* (United

doi:10.6342/NTU202502665

States Patent No. US11596517B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Meissner, T. B., Ferreira, L. M. R., Strominger, J. L., & Cowan, C. A. (2024a). *Universal donor stem cells and related methods* (United States Patent No. US12031154B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Meissner, T. B., Ferreira, L. M. R., Strominger, J. L., & Cowan, C. A. (2024b). *Universal donor stem cells and related methods* (United States Patent No. US12110500B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Meissner, T. B., Ferreira, L. M. R., Strominger, J. L., & Cowan, C. A. (2024c). *Universal donor stem cells and related methods* (United States Patent No. US12031155B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Miklas, J., Radisic, M., Thavandiran, N., Vasconcelos, S., Xiao, Y., Zhang, B., & Zhao, Y. (2019). *Compositions and methods for making and using three-dimensional tissue systems* (United States Patent No. US10254274B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Mohler, K. M., Levitsky, H. I., & SATHER, B. (2020). *Engineered cells for adoptive cell therapy* (United States Patent No. US10786533B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moore, G., Bernett, M., Rashid, R., & Desjarlais, J. (2020). *Heterodimeric proteins* (United States Patent No. United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moore, G., Desjarlais, J., & Chu, S. (2019). *Heterodimeric antibodies that bind CD3 and PSMA* (United States Patent No. US10227410B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moore, G., Desjarlais, J., Chu, S., & Lee, S.-H. (2019). *Trispecific antibodies* (United States Patent No. US10428155B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Morgan, R., & Friedman, K. (2022). *BCMA chimeric antigen receptors* (United States Patent No. US11351236B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moriarity, B., Webber, B., Choudhry, M., Rosenberg, S. A., Palmer, D. C., & Restifo, N. P. (2023). *Intracellular genomic transplant and methods of therapy* (United States Patent No. US11642374B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moriarity, B., Webber, B., Choudhry, M., Rosenberg, S. A., Palmer, D. C., & Restifo, N. P. (2024). *Intracellular genomic transplant and methods of therapy* (United States Patent No. US11903966B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moriarity, B., Webber, B., Largaespada, D., Choudhry, M., & Rosenberg, S. A. (2024). *Intracellular genomic transplant and methods of therapy* (United States Patent No. US11925664B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Moriarity, B., Webber, B., McIvor, R. S., Choudhry, M., Rosenberg, S. A., Palmer, D. C., & Restifo, N. P. (2019). *Intracellular genomic transplant and methods of therapy* (United States Patent No. US10166255B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Muik, A., Swanson, K. A., Yang, Q., Cai, H., Sahin, U., & Modjarrad, K. (2024). *Coronavirus vaccine* (United States Patent No. US11878055B1). United States

doi:10.6342/NTU202502665

Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Murray, M. M. (2023). *Collagen scaffolds* (United States Patent No. US11826489B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Musunuru, K., Cowan, C. A., & Rossi, D. J. (2019). *Therapeutic uses of genome editing with CRISPR/Cas systems* (United States Patent No. US10208319B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Nasert, M. A., Stoffel, F., Williams, P. R., & Callahan, A. (2023). *Cartilage-derived implants and methods of making and using same* (United States Patent No. US11806443B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Nasert, M. A., Stoffel, F., Williams, P. R., & Callahan, A. (2024). *Cartilage-derived implants and methods of making and using same* (United States Patent No. US11938245B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Naso, M., Carton, J., Wheeler, J., & Borges, L. (2023). *Artificial cell death polypeptide for chimeric antigen receptor and uses thereof* (United States Patent No. US11661459B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Nicholas, C. R., Rubenstein, J. L., Kriegstein, A. R., & Alvarez-Buylla, A. (2018). *In vitro production of medial ganglionic eminence precursor cells* (United States Patent No. US10100279B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Nukaya, D., Eiraku, M., Kinose, Y., Onishi, A., Takahashi, M., & SASAI, Y. (2024). *Method for producing retinal tissues* (United States Patent No. US12090252B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Oakes, B., Higgins, S., Spinner, H., Denny, S., Staahl, B. T., Taylor, K., Baney, K., Colin, I., & Adil, M. (2023). *Engineered proteins* (United States Patent No. US11560555B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Oakes, B., Higgins, S., Spinner, H., Denny, S., Staahl, B. T., Taylor, K., Baney, K., Colin, I., & Adil, M. (2024). *Guide scaffolds* (United States Patent No. US12084692B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Osterloh, I., Wicker, P., Braeckman, R., Soni, P., & Manku, M. (2019). *Methods of treating mixed dyslipidemia* (United States Patent No. US10220013B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
PARK, S., Vong, Q., SATHER, B., Ryu, B., Lajoie, M., MOFFETT, H., Weitzner, B., SONG, Y., BOYKEN, S., Sharma, N., Potluri, S., & BOLDAJIPOUR, B. (2024). *ROR1 targeting chimeric antigen receptor* (United States Patent No. US12144827B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Park, S. W., Kim, Y. M., Jung, J. S., & Rhee, Y.-H. (2024). *Method of producing natural killer cells and composition for treating cancer* (United States Patent No. US12098388B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Peterson, Q. P., Pagliuca, F. J., Melton, D. A., Millman, J. R., Segel, M. S., & Gurtler, M. (2018). *SC-β cells and compositions and methods for generating the same* (United States Patent No. US10030229B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Png, Y. T., Vinanica, N., Kamiya, T., & Campana, D. (2022). *Blockade of CD7 expression and chimeric antigen receptors for immunotherapy of T-cell malignancies* (United

doi:10.6342/NTU202502665

States Patent No. US11440958B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Png, Y. T., Vinanica, N., Kamiya, T., & Campana, D. (2024). *Blockade of CD7 expression and chimeric antigen receptors for immunotherapy of T-cell malignancies* US11945865B2).
Popelka, M. (2023). *Inbred corn line CD9* (United States Patent No. US11716945B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Popovic, M., Onal, C., Effraimidis, D., Jennings, B., McCarthy, G. D., & Corso, N. (2024). *Actuators and methods of use* (United States Patent No. US11925594B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Porteus, M. H., Hendel, A., Clark, J., Bak, R. O., Ryan, D. E., Dellinger, D. J., Kaiser, R., & Myerson, J. (2022). *Chemically modified guide RNAS for CRISPR/Cas-mediated gene regulation* (United States Patent No. US11535846B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Porteus, M. H., Hendel, A., Clark, J., Bak, R. O., Ryan, D. E., Dellinger, D. J., Kaiser, R., & Myerson, J. (2023). *Compositions comprising chemically modified guide RNAs for CRISPR/Cas-mediated editing of HBB* (United States Patent No. US11851652B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
RAUCH, S., GROSSE, H. W., & Petsch, B. (2022). *Coronavirus vaccine* (United States Patent No. US11241493B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Rezania, A., & Ramos-Zayas, R. (2020a). *Universal donor cells* (United States Patent No. US10724052B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Rezania, A., & Ramos-Zayas, R. (2020b). *Universal donor cells* (United States Patent No. US10865424B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Rhodes, C. S., & Shimko, D. A. (2024). *Adjustable bone implant for enclosing bone material* (United States Patent No. US12178941B2/). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Rios, D., Mande, P., Viney, J. L., Higginson-Scott, N., Otipoby, K. L., Borthakur, S., Alioto, S., & Edwards, L. J. (2024). *Tissue targeted immunotolerance with a CD39 effector* (United States Patent No. US11981715B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Rogers, C., Dooris, A., Fatyol, P. J., Lionetto, M., Naughton, R. J., & Hawkins, J. R. (2019). *Intervertebral disc* (United States Patent No. US10238500B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Sack, J. A. (2021). *Implant with improved flow characteristics* (United States Patent No. US10940015B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Sack, J. A. (2024). *Implant with improved flow characteristics* (United States Patent No. US11951018B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Sadelain, M. W. J., Eyquem, J. G. A. F., & Mansilla-Soto, J. (2022). *Transgenic T cell and chimeric antigen receptor T cell compositions and related methods* (United States Patent No. US11377637B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Sahin, U., Güler, A., Kuhn, A., Muik, A., Vogel, A., Walzer, K., Witzel, S., Hein, S., & Türeci, Ö. (2023). *Coronavirus vaccine* (United States Patent No.

doi:10.6342/NTU202502665

US11547673B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Sahin, U., Güler, A., Kuhn, A., Muik, A., Vogel, A., Walzer, K., Witzel, S., Hein, S., & Türeci, Ö. (2024). *Coronavirus vaccine* (United States Patent No. US12133899B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Sakoda, R. E. V., Restifo, N., Klausner, R. D., Huang, Y., Maeda, T., Tamaoki, N., & Yamazaki, Y. (2024). *Methods for making, compositions comprising, and methods of using rejuvenated T cells* (United States Patent No. US12091682B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Schlachter, K. W., Shimko, D. A., Kalpakci, K., Vasquez, E., Kaes, D. R., & Bhattacharyya, S. (2019). *Milled bone graft materials and methods of use* (United States Patent No. US10368930B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Schrum, J. P., Siddiqi, S., & Ejebe, K. (2018). *Modified nucleosides, nucleotides, and nucleic acids, and uses thereof* (United States Patent No. US10064959B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Semler, E., Callahan, A., Canales, J., Carroll, K., Dasgupta, A., & Shikhanovich, R. (2018). *Tissue-derived tissuegenic implants, and methods of fabricating and using same* (United States Patent No. US10130736B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Serber, Z., Dean, E. J., Manchester, S., Gora, K., Flashman, M., Shellman, E., Kimball, A., Szyjka, S., Frewen, B., Treynor, T., & Bruno, K. S. (2021). *Automated system for HTP genomic engineering* (United States Patent No. US10883101B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Serber, Z., Dean, E. J., Manchester, S., Gora, K., Flashman, M., Shellman, E., Kimball, A., Szyjka, S., Frewen, B., Treynor, T., & Bruno, K. S. (2021). *HTP genomic engineering platform* (United States Patent No. US11208649B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Serber, Z., Dean, E. J., Manchester, S., Gora, K., Flashman, M., Shellman, E., Kimball, A., Szyjka, S., Frewen, B., Treynor, T., & Bruno, K. S. (2022a). *HTP genomic engineering platform* (United States Patent No. US11352621B2). United States Patent and Trademark Offices. https://tiponet.tipo.gov.tw/gpss/

Serber, Z., Dean, E. J., Manchester, S., Gora, K., Flashman, M., Shellman, E., Kimball, A., Szyjka, S., Frewen, B., Treynor, T., & Bruno, K. S. (2022b). *Systems and methods for host cell improvement utilizing epistatic effects* (United States Patent No. US11312951B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Serhan, H., DiMauro, T. M., & Malone, J. D. (2019a). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10420651B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Serhan, H., DiMauro, T. M., & Malone, J. D. (2019b). *In-situ formed intervertebral fusion device and method* (United States Patent No. US10376372B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Sommer, M., MARTINEZ, V., HELM, E. V. D., HAABER, J. K., TORIO, A. D. S., Grøndahl, C., & Clube, J. (2022a). *Treating and preventing microbial infections* (United States Patent No. US11485973B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Sommer, M., MARTINEZ, V., HELM, E. V. D., HAABER, J. K., TORIO, A. D. S., Grøndahl, C., & Clube, J. (2022b). *Treating and preventing microbial infections*

doi:10.6342/NTU202502665

(United States Patent No. US11421227B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Soni, P. (2019). *Methods of reducing the risk of a cardiovascular event in a subject on statin therapy* (United States Patent No. US10278935B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Soni, P. (2020a). *Methods of reducing the risk of a cardiovascular event in a subject at risk for cardiovascular disease* (United States Patent No. US10568861B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Soni, P. (2020b). *Methods of reducing the risk of a cardiovascular event in a subject at risk for cardiovascular disease* (United States Patent No. US10576054B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Soni, P. (2020c). *Methods of reducing the risk of a cardiovascular event in a subject at risk for cardiovascular disease.* (United States Patent No. US10555925B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Stefani, S., & Gander, T. T. (2022). *Simultaneous multiplex genome editing in yeast* (United States Patent No. US11306299B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Suri, V., Li, D. J., Sun, D., Delabarre, B., BALAKRISHNAN, V., Dolinski, B., INNISS, M. C., & OLINGER, G. Y. (2024). *DHFR tunable protein regulation* (United States Patent No. US12104178B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Szalay, A., & Minev, B. (2018). *Smallpox vaccine for cancer treatment* (United States Patent No. US10105436B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Terrett, J. A., Kalaitzidis, D., Dequéant, M.-L., & Padalia, Z. S. (2022). *Methods and compositions for treating cancer* (United States Patent No. US11254912B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Thon, J., & Dykstra, B. (2024). *Compositions and methods for producing megakaryocytes* (United States Patent No. US12060576B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Tian, T., Johnson, C., & Spindler, E. (2020). *Curing for recursive nucleic acid-guided cell editing* (United States Patent No. US10837021B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Trager, J. B., Buren, L. G., Guo, C., Tohmé, M., Chan, I., & Lazetic, A. L. L. (2022). *CD19-directed chimeric antigen receptors and uses thereof in immunotherapy* (United States Patent No. US11253547B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Valamehr, B., Abujarour, R., Lee, T. T., Lan, W., Clarke, R., & Bjordahl, R. (2019). *Genomic engineering of pluripotent cells* (United States Patent No. US10287606B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Valamehr, B., Clarke, R., & Bjordahl, R. (2020). *Methods and compositions for inducing hematopoietic cell differentiation* (United States Patent No. US10858628B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Viney, J. L., & Higginson-Scott, N. (2020). *Targeted immunotolerance* (United States Patent No. US10676516B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/
Viney, J. L., & Higginson-Scott, N. (2022). *Targeted immunotolerance* (United States Patent No. US11466068B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

doi:10.6342/NTU202502665

Viney, J. L., Higginson-Scott, N., Benson, M., & Crane, A. (2021). *Targeted immunotolerance* (United States Patent No. US10961310B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wang, Z., Fang, L., Guo, B., & Zang, J. (2020). *Anti-CD73 antibodies and uses thereof* (United States Patent No. US10584169B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wang, Z., Fang, L., Guo, B., Zang, J., & Yang, Q. (2021). *Anti-CD73 anti-PD-L1 bispecific antibodies* (United States Patent No. US11034771B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wei, G. (2018). *3D printing of mesh implants for bone delivery* (United States Patent No. US10064726B1). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Weinschenk, T., Mahr, A., Fritsche, J., Mueller, P., Wiebe, A., & Kutscher, S. (2018). *Peptides and combination of peptides for use in immunotherapy against hepatocellular carcinoma (HCC) and other cancers* (United States Patent No. US10064926B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Weinschenk, T., Mahr, A., Fritsche, J., Mueller, P., Wiebe, A., & Kutscher, S. (2023). *Peptides and combination of peptides for use in immunotherapy against Hepatocellular carcinoma (HCC) and other cancers* (United States Patent No. US11786583B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Weinschenk, T., Schoor, O., & MAHR, A. (2024). *Peptides and combination of peptides for use in immunotherapy against non-small cell lung cancer and other cancers* (United States Patent No. US12168044B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Weinschenk, T., Walter, S., FRITSCHE, J., SONG, C., & Singh, H. (2018). *Immunotherapy against several tumors, such as lung cancer, including NSCLC* (United States Patent No. US10071148B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Weinschenk, T., Walter, S., Fritsche, J., Song, C., & Singh, H. (2023). *Immunotherapy against several tumors including lung cancer* (United States Patent No. US11814446B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Weinschenk, T., Walter, S., Fritsche, J., Song, C., & Singh, H. (2024). *Immunotherapy against several tumors including lung cancer* (United States Patent No. US11866517B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wells, J., & McCracken, K. (2021). *Methods for the in vitro manufacture of gastric fundus tissue and compositions related to same* (United States Patent No. US11066650B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wells, J. M., & McCracken, K. W. (2021). *Methods and systems for converting precursor cells into gastric tissues through directed differentiation* (United States Patent No. US11053477B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wells, J. M., & Munera, J. O. (2023). *Colonic organoids and methods of making and using same* (United States Patent No. US11767515B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wells, J. M., Watson, C. L., Munera, J. O., Mahe, M. M., Helmrath, M. A., & Workman,

doi:10.6342/NTU202502665

M. J. (2023). *Method of making in vivo human small intestine organoids from pluripotent stem cells* (United States Patent No. US11584916B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Williams, J., Nguyen, M., Yao, A., Santoro, S., Cooper, A., Gagnon, J., Litterman, A., Khan, O., Bezman, N., Harris, K., CHAUDHRY, H. K. M., & Allen, N. (2024). *Immune cells having co-expressed shRNAS and logic gate systems* (United States Patent No. US12037407B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wilson, N. S., Morin, B. M., Findeis, M. A., Mundt, C. A., van Dijk, M., Chand, D. S., Savitsky, D. A., Underwood, D. J., & Ignatovich, O. (2021). *Anti-CD137 antibodies and methods of use thereof* (United States Patent No. US11098117B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wilson, N. S., Waight, J. D., Jennings, S. M., Ignatovich, O., BriendB, E. C. P., Morin, e. M., Schon, O., & Campbell, S. (2023). *Anti-CD73 antibodies and methods of use thereof* (United States Patent No. US11692042B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Winston, W., Hicklin, D., Bhaskar, V., Evnin, L., Baeuerle, P., Salmeron Garcia, J. A., Brodkin, H., & Seidel-Dugan, C. (2020). *Activatable interleukin 12 polypeptides* (United States Patent No. US10696723B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Wu, C.-Y., Onuffer, J., & Lim, W. A. (2018). *Chimeric antigen receptor and methods of use thereof* (United States Patent No. US10105391B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Xiao, Y., Wilson, N. S., Morin, B. M., Findeis, M. A., Mundt, C. A., van Dijk, M., Chand, D. S., Savitsky, D. A., Underwood, D. J., & Ignatovich, O. (2022). *Anti-CD137 antibodies and methods of use thereof* (United States Patent No. US11242385B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Yao, Y., Li, Y., Wei, Y., Zhu, S., Yao, X., & Huang, J. (2021). *Combined chimeric antigen receptor targeting CD19 and CD20 and application thereof* (United States Patent No. US11207349B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Zhang, F., Gao, L., Zetsche, B., & Slaymaker, I. (2019). *Crispr enzyme mutations reducing off-target effects* (United States Patent No. US10494621B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Zhang, F., Zetsche, B., Gootenberg, J. S., Abudayyeh, O. O., & Slaymaker, I. (2021). *CRISPR enzymes and systems* (United States Patent No. US11091798B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Zhang, F., Zetsche, B., Gootenberg, J. S., Abudayyeh, O. O., & Slaymaker, I. (2024). *Crispr enzymes and systems* (United States Patent No. US12091709B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Zhang, F., Zetsche, B., Slaymaker, I., Gootenberg, J., & Abudayyeh, O. O. (2020). *CRISPR enzymes and systems* (United States Patent No. US10669540B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

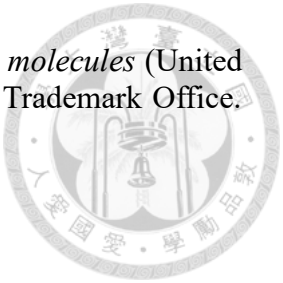
Zhang, H., Shi, H., Shen, L., Cao, W., & Liu, L. (2023). *Engineered immune cells targeting BCMA and their uses thereof* (United States Patent No. US11840575B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Zhao, Y., REN, J., Liu, X., & June, C. H. (2021). *Altering gene expression in modified T cells and uses thereof* (United States Patent No. US11203758B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/

Zhao, Y., Shedlock, D. J., June, C. H., & Liu, X. (2024). *Enhanced antigen presenting*

doi:10.6342/NTU202502665

ability of RNA car T cells by co-introduction of costimulatory molecules (United States Patent No. US12162922B2). United States Patent and Trademark Office. https://tiponet.tipo.gov.tw/gpss/



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Appendix A

Semi-Structured Interview Protocol for CGT Manufacturers in Taiwan

Table A 1

Interview Protocol for Taiwanese CGT Manufacturers

Thematic Sections	Questions
Basic Info (10 min)	1. Which CGT product did you choose for your company? Why? 2. Continuing from the above, what are the potentials of this technology? Could you please elaborate on what kind of technology development or clinical cooperation the company has invested in the past few years? Will the main challenges in the future be technology, regulations or market acceptance?
Technology and Clinical Application (15 min)	3. Which of the six CGT technologies mentioned in this study do you think is most likely to be accepted by the clinic or the market? Why? 4. Based on the above, from what perspectives would you judge whether it is worth investing? Why?
Cost and Payment (15 min)	5. Why is the cost of CGT so high? In which part do you think the investment in CGT is much greater than that of other drugs? (Such as compliance with regulatory standards, production line construction, clinical trials, human resources, etc.) 6. Do you hope that your CGT products can be included in the health insurance? Why? a. If the answer is yes, have you applied for it and what was the result of the application? b. If the answer is no, have you considered allowing commercial insurance to join the payment system? Do you have any suggestions for the inclusion of commercial insurance? 7. What is your view on payment mechanisms such as outcome-based reimbursement, risk sharing, or advance funds? Are they feasible in Taiwan?
Policy and Industry (15 min)	8. Do you think the current policy support for CGT is sufficient? Which areas require improvement?
Other (5 min)	9. Do you feel optimistic about CGT development in Taiwan over the next 10 years? 10. What do you think are Taiwan's advantages in the international CGT market? How can it contribute?

Note. Compiled by the researcher.

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Appendix B

GPT-Assisted Theme Summarization for Patent Clusters

To enhance the interpretability of patent clusters identified through citation network analysis, GPT-4 was used to assist in summarizing the thematic focus of each group. This appendix documents the input data, prompt design, generated outputs, and post-review notes for each cluster. All results were manually reviewed and revised to ensure semantic accuracy and conceptual validity.

B.1 Prompt Template Used for Theme Generation

Prompt:

The following are the titles of a group of patents identified from a citation-based cluster. Please analyze the content and provide:

1. A concise theme label (5–10 words);
2. A short description (2–3 sentences) summarizing the main technical focus of the group.

B.2 Example: Cluster (j)

Cluster (j) from the patent citation network of MSC is selected as an example to demonstrate the utility of GPT-4 in the study.

B.2.1. Input Data and Result

The input data is displayed in **Table B 1**, and the result of GPT's output is displayed in **Table B 2**.

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Table B 1

The Input Titles of Cluster (j)

No.	Patent Titles
1	Systems and methods for targeted integration and genome editing and detection thereof using integrated priming sites
2	RNA-guided nucleic acid modifying enzymes and methods of use thereof
3	Type V CRISPR/Cas effector proteins for cleaving ssDNAs and detecting target DNAs
4	Methods and compositions for treatment of a genetic condition
5	Nuclease-mediated genome editing of primary cells and enrichment thereof
6	Crispr enzyme mutations reducing off-target effects
7	Compositions comprising chemically modified guide RNAs for CRISPR/Cas-mediated editing of HBB
8	CRISPR enzyme mutations reducing off-target effects
9	Engineered CRISPR-Cas9 nucleases with altered PAM specificity
10	Engineered CRISPR-Cas9 nucleases with altered PAM specificity
11	Class 2 CRISPR/Cas compositions and methods of use
12	Pharmaceutical compositions comprising gene-corrected primary cells
13	Nuclease-mediated genome editing of primary cells
14	Chemically modified guide RNAS for CRISPR/Cas-mediated gene regulation
15	Chemically modified guide RNAs for CRISPR/CAS-mediated gene regulation
16	Engineered Cas9 nucleases
17	Engineered class 2 type V CRISPR systems
18	Guide scaffolds
19	RNA-guided nucleic acid modifying enzymes and methods of use thereof
20	RNA-guided nucleic acid modifying enzymes and methods of use thereof
21	Engineered proteins
22	CASZ compositions and methods of use
23	CRISPR-Cas12J effector polypeptides and methods of use thereof
24	CRISPR-Cas effector polypeptides and methods of use thereof
25	CRISPR-Cas effector polypeptides and methods of use thereof
26	CRISPR-Cas effector polypeptides and methods of use thereof
27	CasZ compositions and methods of use
28	Modified cells comprising CRISPR systems
29	CasZ compositions and methods of use
30	RNA-guided nucleic acid modifying enzymes and methods of use thereof
31	Cpf1 complexes with reduced indel activity
32	Crispr enzymes and systems
33	Crispr enzymes and systems
34	CRISPR enzymes and systems

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Table B 1 (continued)

No.	Patent Titles
35	CRISPR enzymes and systems
36	Crispr enzymes and systems
37	CRISPR enzymes and systems
38	CRISPR enzymes and systems
39	CRISPR enzymes and systems
40	Engineered Cas9 nucleases
41	Polynucleotide encoding modified CAS9 protein
42	Modified Cas9 protein and use thereof
43	Delivery methods and compositions for nuclease-mediated genome engineering
44	Methods and compositions for treatment of a beta thalessemia
45	Guide RNAs with chemical modification for prime editing
46	CasZ compositions and methods of use
47	Type V CRISPR-Cas systems and use thereof
48	Protected guide RNAS (pgRNAS)
49	Materials and methods for treatment of Spinocerebellar Ataxia Type 1 (SCA1) and other Spinocerebellar Ataxia Type 1 Protein (ATXN1) gene related conditions or disorders
50	Type V CRISPR/Cas effector proteins for cleaving ssDNAs and detecting target DNAs
51	Type V CRISPR/Cas effector proteins for cleaving ssDNAs and detecting target DNAs
52	Crispr enzyme mutations reducing off-target effects
53	Delivery methods and compositions for nuclease-mediated genome engineering

Note. Data compiled by the researcher from the Global Patent Search System (GPSS), 2025.

Table B 2

The Output Result of GPT-4

Theme Label	Next-Generation CRISPR Systems and Precision Genome Editing Technologies
Summary Description	This patent cluster centers on advancements in CRISPR-based genome editing tools, especially Class 2 systems like Cas9, Cas12 (Cpf1), and Cas12J. The inventions include engineered nucleases with improved PAM specificity and reduced off-target activity, chemically modified guide RNAs for enhanced editing precision, and delivery methods for therapeutic genome correction in primary cells. Notably, the group reflects substantial innovation in developing Type V CRISPR effectors (e.g., Cas12 variants and CasZ) and their application in diagnostics and disease treatment, including β-thalassemia and spinocerebellar ataxia.

Note. Data compiled by the researcher from GPT-4.

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B.3 Final Cluster Labels

. Minor edits were made to avoid overly broad phrases and ensure consistency with clinical terminology.

Table B 3 displays the label results generated by GPT-4. Minor edits were made to avoid overly broad phrases and ensure consistency with clinical terminology.

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Table B 3

GPT-generated and Final Labels for Each Patent Cluster

CGT	Cluster ID	GPT Label	Manual Final Label
AAV	a	CAR-T Cell Therapies with Gene Editing and Target Modulation	
	b	Spatial Omics and Immune Profiling Technologies	
	c	mRNA Vaccines and Delivery Platforms for Infectious Diseases	
CAR-T	d	Next-Generation CAR-T and Engineered Immune Cell Therapies	CAR-T and Engineered Immune Cell Therapies
CRISPR	e	Advanced Genome Engineering and Therapeutic Applications of CRISPR	
	f	Elite Soybean Cultivar Development and Breeding	
	g	Maize Hybrid and Inbred Varieties for Seed Production	
MSC	h	Tissue-Derived Biomaterials and Regenerative Implants	
	i	Peptide-Based Personalized Cancer Immunotherapies	
	j	Next-Generation CRISPR Systems and Precision Genome Editing Technologies	CRISPR Systems and Precision Genome Editing Technologies
	k	Cell Engineering Platforms for Regenerative and Immuno-Oncology Therapies	
	l	Soft Tissue Fixation and Ligament Repair Technologies	
	m	Expandable and In-Situ Intervertebral Fusion Devices	
NK Cell	n	Next-Generation CAR and Immune Cell Therapies for Cancer	CAR and Immune Cell Therapies for Cancer
	o	Omega-3 Therapies for Cardiovascular and Lipid Disorders	
	p	TIGIT and CD137 Immune Checkpoint Antagonists for Cancer Immunotherapy	
iPSC	q	Gene and Cell Therapy Platforms for Regenerative Medicine and Immunotherapy	
	r	Pluripotent Stem Cell-Derived Therapeutics and Engineered Cell Platforms	

Note. Data compiled by the researcher from GPT-4.

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B.4 Disclaimer on GPT Usage

The outputs presented above were generated using GPT-4 (OpenAI, 2024) based on carefully structured prompts. While the model was used to enhance efficiency and consistency in thematic interpretation, all content was subject to human review and final approval. The model's outputs are not deterministic and may vary slightly upon repetition; only reviewed and verified results were retained.

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