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Review

Human gene therapy: A patent analysis

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ABSTRACT

Although seen as a revolution in modern science, gene therapy has been plagued by failed clinical trials and controversial ethics in the last thirty years. Moreover, there is no comprehensive, in-depth, high-quality analysis of global gene therapy patents. This paper proposes a method to correctly retrieve patents to address the issue and use it for the patent landscape. The results show the global patent landscape of gene therapy, with the United States dominating the field, while China has emerged as a leader in recent years. For various reasons, the EU, Korea, and Japan lag in the development of patented technologies. China has edged closer to the US in both live and indefinite patents, with the Chinese Academy of Military Medical Sciences and the Chinese Academy of Sciences leading the way, surpassing primary applicants such as the US Department of Health and Human Services, the University of California, and the University of Pennsylvania. The study also reveals four broad categories of technologies that have been extensively studied in gene therapy: basic biology of the gene and diseases, diseases being treated, gene delivery methods, and potential adverse events. What is more, Adeno-Associated Virus, Retrovirus, and Lentivirus are the most prevalent gene therapy delivery vectors after 2014. The industrial development trend revealed in this paper can provide an evidence-based basis for scientific research management and decision-making.

1. Introduction

In 2020, Lu et al. delivered the first clustered regularly interspaced short palindromic repeats (CRISPR)-edited T cell therapy for patients with refractory non-small-cell lung cancer (Lu et al., 2020). This is a milestone that marks an upgrade to the next generation of gene therapy (Zeballos and Gaj, 2021). Gene therapy is an emerging experimental treatment that delivers functional genes into the human body to counter or replace malfunctioning genes, thus curing diseases without pharmacological intervention, radiotherapy, or surgery (Dunbar et al., 2018; Nelson et al., 2016). Gene therapy is considered promising and applicable to a wide range of diseases, with the first approved human gene therapy trial conducted by Rosenberg et al. in 1989, using retroviral vectors to deliver the gene coding for resistance to neomycin to patients with advanced melanoma (Rosenberg et al., 1990). Gene therapies have faced severe setbacks in 1999–2002 (Kumar et al., 2016), but the resurgent interest in offering gene therapy-based treatments from 2015 is one of the most defining pharmaceutical industry developments (Goswami et al., 2019; Salzman et al., 2018). It is expected to have far-reaching implications on curing dangerous diseases in the future and benefit both clinical trials and the pharmaceutical industry immensely (Anguela and High, 2019; High and Roncarolo, 2019).

The progress and setbacks of gene therapy are closely linked to the R&D endeavor of industry participants, whose frustrations in the research process have reconfigured its innovation locus (Kapoor and Klueter, 2020), prompting researchers to develop new gene delivery vectors and gene editing technologies (Ledley et al., 2014). Science quality and patent value are closely related, and in this sense (Ahmadpoor and Jones, 2017; Poege et al., 2019), it is imperative to study the industrial development characteristics (Hohberger, 2016). Patent landscapes enable researchers and policymakers to quantify intellectual property characteristics, such as innovation, knowledge spillovers, collaboration, and technology space (Grant et al., 2014; Smyth et al., 2013). However, there are shreds of evidence for low reporting quality in patent landscapes (Smith, 2020), such as searching patents only by keywords, or the misusing of patent classification system. Moreover, A

Abbreviations: DI, Derwent Innovation Database; MC, DWPI manual codes; IPC, International Patent Classification; EMA, European Medicines Agency; US HHS, the US Department of Health and Human Services; AMMS, the China Academy of Military Medical Sciences; INSERM, Institut National de la Santé et de la Recherche Médicale; CNRS, Centre national recherche Scientifique; AV, Adenovirus; AAV, Adeno-Associated Virus; LV, Lentivirus; HSV, Herpes Viruses.

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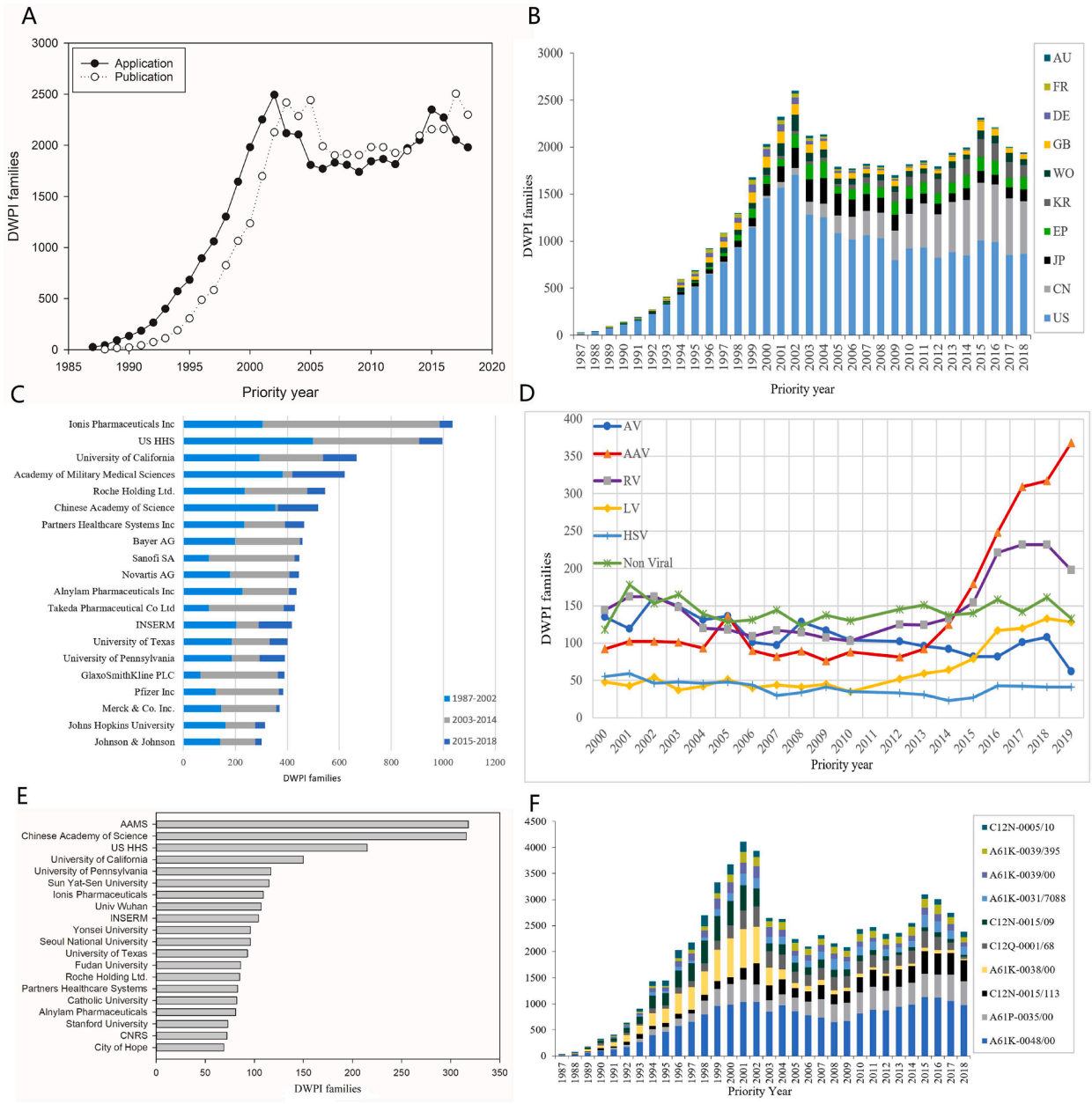

Fig. 1. Gene therapy patenting trends. a. Annual patent trends related to gene therapy; b. Source location of annual patent applications from 1987 to 2018; c. Top 20 applicants in gene therapy from 1987 to 2019 with time chips; d. Trending of viral and non-viral gene delivery methods since 2000; e. Top 20 organizations in gene therapy with legal status alive & indeterminate; f. Distribution of main technology areas according to IPC. IPC codes can be accessed at https://www.wipo.int/classifications/ipc/en/: A61K 48/00: Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases; Gene therapy. A61P 35/00: Antineoplastic agents. C12N 15/113: Non-coding nucleic acids modulating the expression of genes. A61K 38/00: Medicinal preparations containing peptides. C12Q 1/68: Measuring or testing processes involving enzymes, nucleic acids or microorganisms; Compositions therefor; Processes of preparing such compositions – involving nucleic acids. C12N 15/09: vectors Recombinant DNA-technology. A61K 31/7088: Compounds having three or more nucleosides or nucleotides. A61K 39/00: Medicinal preparations containing antigens or antibodies. A61K 39/395: Antibodies; Immunoglobulins; Immune serum. C12N 5/10: Cells modified by introduction of foreign genetic material.

comprehensive and in-depth analysis of the global gene therapy patent landscape is not yet available in PubMed, Web of Science, or Scopus. This paper addresses deficiencies by giving guidance on patent analysis's practical process and provides a patent landscape for the global gene therapy industry.

2. Data sources and search methods

Due to definitional or ethical issues, such methods as obtaining new varieties of plants or animals, treatment of plant and animal diseases, part of the gene-transfer research altering the germline or generating new embryos, was excluded from this study.

The method of conducting patent searching is vital in presenting a patent landscape. Keywords are useful in searching for patent information, but there may be a misspelling, synonyms, or scientific names. Searching patent documents by patent classification, which is language-independent, can improve the coverage and help overcome some of the pitfalls of searching by keywords alone. On the other hand, patent classifications contain many data noises and a small portion of mistakenly classified documents, which incurs the necessity for combining

Table 1
Global patent layouts of the seven major source countries.

	WO	US	EP	AU	JP	CN	CA	KR	DE
US	18,638	20,548	11,073	11,073	7861	4262	5593	2745	1386
CN	500	218	141	141	94	7218	46	44	7
JP	1823	1186	1011	1011	3095	491	292	343	129
KR	617	452	260	260	233	207	53	1853	16
GB	1538	1084	1158	1158	795	391	387	208	241
DE	539	387	483	483	308	100	114	73	684
FR	489	347	410	410	314	93	137	102	162

keywords in data retrieval and further data cleaning. So the combination of keywords and classifications, including International Patent Classification (IPC) and DWPI Manual Code (MC), is a more favorable solution. The IPC covers nearly every imaginable field of technology. The DWPI Manual Codes is a hierarchical indexing system intended for a patent retrieval and analysis tool.

After extensive patent search and analysis, we devised a complex search query: ((Q1 OR Q2 OR Q3) NOT Q4). Q1 is purely IPC codes and MC that match the definition of gene therapy. Q2 is a combination of IPC/MC and keywords to identify patents not included in Q1. Q3 uses keywords for a supplement. Furthermore, Q4 is for data cleaning, which is the most challenging part of the research. Irrelevant records were removed, for instance, plant or animal gene editing and germline altering therapy. The detailed search formula is put in the appendix as it is too complicated and lengthy.

This study analyzes the patent literature on gene therapy in the Derwent Innovation Database (DI). The search was performed on 21 January 2021 and retrieved 47,533 DWPI families (42,344 INPADOC families), with more than 82,421 inventors, 9,225 ultimate parent companies, 56 priority countries/locations identified. The Derwent Data Analyzer was used to analyze data from 1987 to 2018 to provide comparative information about gene therapy patents, focusing on annual trends in the field, major R&D countries, principal applicants, and key technologies represented by gene vectors. As there is a time lag of 18 months between the priority date and publication date, the 2019–2020 figures are for references only. The patent landscape is carried out based on DWPI patent families. DWPI patent families follow a strict "invention-record" principle, i.e., one invention shares exact priorities with each and every other family member, and each member of a DWPI patent family is essentially the same in terms of technical content. In contrast, the INPADOC families only require that any member have a shared priority to another, which allows for a broad family definition that includes divisions, continuations, and continuations in part. Therefore, the use of DWPI patent families allows a more refined distinction between different technical contents.

3. Results and discussion

Based on this data, we describe gene therapy's global landscape's main features, including trends in patent filing and publication, applicants, inventors, technology highlights, and trends in gene therapy delivery systems.

3.1. Annual distribution of global patent application/publication

Since the first gene therapy trial in humans in 1990, science has increased understanding of the basic biology of the diseases being treated, the various methods used for gene delivery, and the potential adverse events that can be encountered (Collins and Gottlieb, 2018).

The trending patent filing activity (Fig. 1a) echoed with successes and setbacks faced with gene therapy. Gene therapy was in its infancy from 1987 to 1993, and patenting filing activities were relatively low. 1993–2002 saw a boom in patent applications, reached its zenith in 2002. However, the seed of tragedy was buried two years ago. In September 1999, the death of Jesse Gelsinger, a research participant in an adenoviral vector gene therapy clinical trial, brought safety and efficacy into sharp focus and set the entire industry in nearly Stagnation (Anguela and High, 2019). As a result, the patent filing was relatively at a low level between 2003 and 2012, coinciding with the number of clinical trials conducted worldwide in the meantime (Goswami et al., 2019).

It was not until 2012 before patent filings became active again when two landmark events brought the whole field a quantum leap forward. One was the discovery and development of the CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 gene-editing system, which brought explorations into gene-editing approaches and clinical trials back to life (Barrangou and Doudna, 2016). The other was Alipogene tiparvovec (Glybera)'s approval by the European Medicines Agency (EMA), a gene therapy drug designed by UniQure to treat lipoprotein esterase deficiency. It was the world's first gene therapy drug for a genetic disease (Gaudet et al., 2016). Patent activities kept booming after 2012 but have not surpassed the zenith of 2002 yet. There are still way ahead.

3.2. Global distribution of major countries/regions

The top five countries in terms of the number of patents produced are the US, China, Japan, the Republic of Korea, and the UK, which account for 87% of the world's total patents. The US ranks first in the world in terms of the number of patents, far ahead of other countries, accounting for 56% of the world's total patents (Fig. 1b). China and the Republic of Korea became increasingly active in the field of gene therapy since 2002. Regulatory, social, and policy issues have a significant impact on the development of gene therapy (Soini et al., 2008). In the European Union case, its gene patent policy severely limits the patentability of gene modification technology (Cole, 2015; Gaisser et al., 2009).

By analyzing the earliest priority countries for DWPI families, we found seven major patent source countries: the US, China, Japan, the UK, Republic of Korea, Germany, and France (Table 1). The US dominates almost all countries' patenting but emphasizes more on the EU and Japan than on China. Japan and UK are in the second echelon. They both are major technology exporters and pay more attention to overseas markets. The Republic of Korea, Germany, and France are in the third echelon, and no significant differences between them. China's domestic application volume is 7,218, accounting for 51% of its total 14,060 DWPI families, which means foreign assignees filed 49% of its patents.

3.3. Top organizations worldwide

Fig. 1b shows the principal applicants in the gene therapy patent application. Most of the top 20 assignees were from the US. Ionis Pharmaceuticals (named Isis Pharmaceuticals until December 2015) and the US Department of Health and Human Services (US HHS) were the top two applicants. The patenting activity of Ionis Pharmaceuticals declined significantly after 2012.

From 2003 onwards, China filed many applications, and this was in coincidence with China becoming the first nation to approve Gendicine, a gene therapy for head and neck cancer in the same year. Top assignees were the China Academy of Military Medical Sciences (AMMS), the Chinese Academy of Science, and many more universities. China and the

Table 2
Top 20 invertors with affiliation and active time range.

Records	Person	Organization	Year Range
220	Dobie Kenneth W.	Ionis Pharmaceuticals	2001–2011
205	Bennett Clarence Frank	Ionis Pharmaceuticals	1990–2017
186	Golz Stefan	Bayer AG	2002–2009
184	Brüggemeier Ulf	Bayer AG	2002–2009
167	Freier Susan M.	Ionis Pharmaceuticals	1991–2018
162	Manoharan Muthiah	Alnylam Pharmaceuticals	1990–2018
162	Monia Brett P.	Ionis Pharmaceuticals	1991–2016
158	Geerts Andreas	Bayer AG	2002–2006
129	Cowsert Lex M.	Ionis Pharmaceuticals	1989–2003
119	Mcswiggen James	Marina Biotech Inc	1992–2013
113	Agrawal Sudhir	Idera Pharmaceuticals Inc	1986–2016
109	LI Hong-Liang	Univ Wuhan	2007–2019
107	Mc Swiggen James	Alnylam Pharmaceuticals	1997–2007
106	Swayze Eric E.	Ionis Pharmaceuticals	1996–2017
100	YANG Cheng-Gang	AMMS	2015–2019
99	Beigelman Leonid	Alnylam Pharmaceuticals	1994–2017
96	Metzger W. James	Univ Pennsylvania	1987–2018
87	Nakamura Yusuke	OncoTherapy Science Inc	1991–2017
79	Wolff Jon Asher	Roche Holding Ltd	1988–2010
78	Summer Holger	Bayer AG	2002–2006

Table 3
Geographical distribution of each gene delivery vectors.

AV	AAV	RV	LV	HSV	Non-Viral
US (1344)	US (2071)	US (1923)	US (694)	US (622)	US (1256)
China (549)	China (288)	China (582)	China (311)	UK (83)	China (974)
Japan (125)	EP (197)	EP (191)	UK (73)	China (61)	Japan (175)
EP (109)	Korea (102)	UK (168)	Korea (69)	EP (43)	EP (136)
UK (95)	UK (94)	Japan (123)	EP (62)	Japan (38)	Korea (113)
Korea (93)	Japan (71)	Korea (119)	Japan (46)	WO (26)	UK (77)
France (74)	WO (60)	WO (92)	WO (34)	Germany (24)	WO (64)
Germany (41)	Germany (59)	France (64)	Germany (16)	Korea (23)	Germany (56)
WO (40)	AU (21)	Germany (56)	France (15)	AU (14)	France (55)
AU (22)	France (19)	Denmark (35)	Spain (12)	France (10)	Russia (51)

Republic of Korea benefited from a certain degree of decline in R&D activity in the US and Europe. At the same time, Japan kept a steady interest in gene therapy from an earlier era of the 1990s up till now.

From 2013 on, AMMS took the lead in patent applications. France kept an active role in gene therapy through its two biggest assignees, Institut National de la Santé et de la Recherche Médicale (INSERM, French National Institute of Health and Medical Research) and National Centre for Scientific Research (Centre national recherche Scientifique, CNRS).

Post-2012 trend in patenting activity suggest that the US is still dominant in gene therapy. China, the Republic of Korea, and France have emerged in this area, but their R&D activities are mainly confined to research organizations. It reveals a certain degree of decline in the industry that biotech firms and large pharmaceutical companies like Bayer, Sinofi, GlaxoSmithKline, and Merck slowed their patenting pace in recent years. At the same time, academic organizations continued to pursue research in gene therapy.

3.4. Top inventor analysis

The top 20 inventors originated from a few pharmaceutical companies (Table 2). Most of them came from Ionis Pharmaceuticals and Bayer AG. Other inventors came from institutions such as Alnylam Pharmaceuticals, Marina Biotech Inc, and Idera Pharmaceuticals Inc. In recent years, active inventors include Freier Susan M., Manoharan Muthiah, Li Hong-Liang, Yang Cheng-gang, and Metzger W. James.

3.5. Distribution of main technology areas

Technology trends can be analyzed by annual IPC (or other patent classification system) trend (Fig. 1f). Before 2002, gene therapy is patenting flourished, with every branch well researched and rapidly growing. 2003 saw a significant blow to the industry, with the most shrinkage occurring in A61K 38/00 (Medicinal preparations containing peptides). C12Q 1/68 (Measuring or testing processes involving enzymes, nucleic acids, or microorganisms) decreased dramatically in recent years. The emphasis shifted to C12N 15/113 (Non-coding nucleic acids modulating genes), which saw steady growth.

3.6. In-depth analysis of patents alive & indeterminate

The legal status analysis revealed that of the total 47,533 DWPI families retrieved, only 22% (10,616) remained alive, 5% (2,362) indeterminate. It implies that innovation in gene therapy is fast, and new technologies are rapidly replacing old ones.

We analyzed the part of patents with legal status alive and indeterminate. It gives a more realistic landscape of the current state of gene therapy patenting. The US is still ahead, with more than 5,000 patent families. China has caught up and is close behind, with more than 4,000 patent filings. The Republic of Korea, with more than 1,000 patent families, was the third-largest country devoted to gene therapy patents. Japan, Germany, Russia, France, India, and others followed behind with fewer applications.

China's AMMS and CAS lead the way in patent applications, and several Chinese universities have filed many applications also. The US has the largest number of applications overall and the largest number of research organizations, including traditional research institutions such as the US HHS, University of California, University of Pennsylvania, University of Texas, and Stanford University, and traditional and emerging pharmaceutical companies such as Ionis Pharmaceuticals and City of Hope. The Republic of Korea and France also have several top universities and research institutions, including Yonsei University, Seoul National University, INSERM, and CNRS (Fig. 1e).

3.7. A comparison of gene delivery methods

Several viral vectors and non-viral gene delivery methods have been developed and found their applications in gene therapy. There are mainly five viral vectors: Adenovirus (AV), Adeno-Associated Virus (AAV), Lentivirus (LV), Retrovirus (RV), and Herpes Viruses (HSV) (Gupta et al., 2020). Non-viral gene delivery methods could be liposomes, cationic polymers, dendrimers, and cell-penetrating peptides (Santana-Armas and Tros de Ilarduya, 2021).

Following the development of the gene therapy industry in general, patenting activities for vectors have been at a relatively low ebb since 1999. In 2012, with the successful approval of Alipogene Tiparvovec, the first gene therapy drug prepared by AAV vectors, AAV vectors had been extensively studied after 2015. The list of successful gene therapy trials using AAV-based vectors continues to grow. AAV vectors are currently the most promising viral vector (Li and Samulski, 2020), with RV Vectors watched closely behind. The patenting activity of AV vectors kept low as it led to the tragedy in 1999. Non-viral vectors became the first choice for research outside of viral vectors after 2001 and have long maintained at the same annual filing level (Fig. 1d).

In terms of applicant location, the US has been leading the way, followed by China's recent surge in vector research and many applications from the UK, Japan, and the Republic of Korea. As shown in Table 3, the US has the highest patent applications for each gene delivery vector and focuses on AAV, RV and LV. China ranks second in

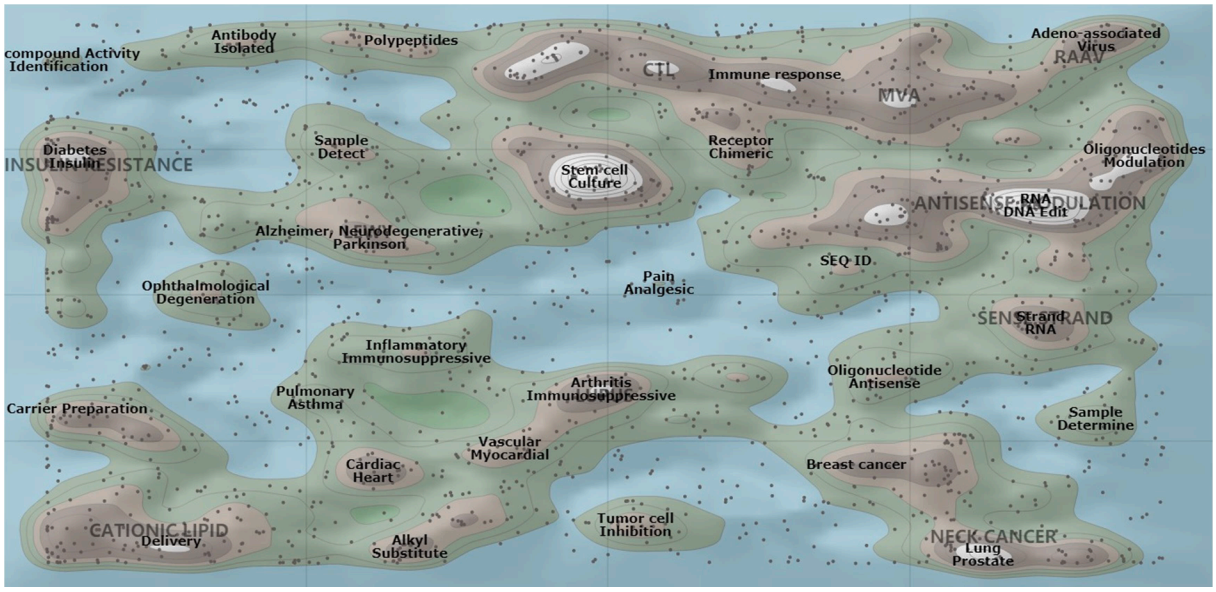

Fig. 2. ThemeScape map of gene therapy.

vectors other than HSV, with the most focus on non-viral delivery vectors, and is the closest to the US in terms of the number of applications. Europe and Japan have lagged significantly behind the US and China in patent applications for various gene delivery vectors.

3.8. Cluster analysis of gene therapy

ThemeScape map, a data analytics tool in Derwent Innovation, conducts cluster analysis of gene therapy to create content maps from literature contents of patent data (Fig. 2). The cluster map, generated by an algorithm that uses keywords from patent documentation to cluster patents, helps identify similar records, cluster those records together, and place those clusters on a map. The patents are organized based on common themes and are grouped as contours on the map to identify high and low patenting activity areas. The snow-capped peaks represent the highest concentrations of patented inventions, and each peak is labeled with binding terms that tie the common themes together. The distance between peaks represents the correlation between patents (Hoo, 2020).

The snow-capped peaks show researchers are active in the areas of stem cells, RNA & DNA editing, cationic lipid vectors, AAV vectors, cancers, et al. Overall, the map shows that four broad categories of technologies were widely studied in the field of gene therapy:

a. Basic biology of the gene and diseases, shown in keywords in the map as antisense modulation, RNA & DNA editing, oligonucleotides modulation, tumor cell inhibition, mevalonate pathway, SEQ ID, sample determine kit.
b. Diseases being treated: various cancers, diabetes, asthma, cardiac diseases, arthritis, Alzheimer's & Parkinson's disease, Lupus.
c. Gene delivery methods: stem cells, cationic lipid, AAV & rAAV, delivery polypeptides, and vector preparation.
d. Potential adverse events: Immune response and immune suppressive treatment.

4. Conclusions

This study's main shortcoming may be that the patents of gene editing-related therapies or CAR T cell therapy are not included in the search formula. Gene editing, including ZFN, TALEN, CRISPR-Cas, base editing, and prime editing, are not generally considered traditional gene therapies and are usually treated independently. Some of the patents on gene transfer technologies that alter germline or produce new embryos were also removed in the search.

This paper gives the main features of the global patent landscape for gene therapy, including trends in patent application and publication, applicants, inventors, technology focus, and trends in gene delivery vectors. The fact that only 27% of patents worldwide have not expired shows a highly dynamic technology area. The US has been a champion and technology pioneer in gene therapy. China has joined the research in the last decade and is rapidly becoming the second-largest patenting nation. EU, Korea, and Japan are significantly behind the US and China in developing patented gene therapy technologies due to differences in national circumstances, regulations and policies, and research strength. In terms of applicants, Ionis Pharmaceuticals and US HHS are the leading institutions in the US. The Chinese Academy of Military Medical Sciences and the Chinese Academy of Sciences are the leading institutions in China, and INSERM and CNRS are the leading institutions in the EU. The US leads in all technology areas, while China focuses on developing non-viral delivery vector technologies.

Due to technical limitations, medical ethics, and regulatory hurdles, gene therapy is still substantially in the clinical trial stage, and there are still very few approved gene therapy drugs (Lapteva et al., 2020; Ma et al., 2020). The era of gene therapy as the mainstay of treatment of diseases seems to have not yet arrived. However, as technology advances and clinical trials progress, more gene therapy drugs are expected to be approved each year. This study provides a panoramic view of gene therapy patent research by proposing a proper methodology and detailed guidance for searching and analyzing patent data. The trend of gene therapy technology revealed in this study echoes the development of clinical trials and the pharmaceutical industry, which will help promote science and human health and guide the formulation of relevant scientific research policies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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