GLOBAL SCIENCE & TECHNOLOGY TRENDS REPORT

GENE AND CELL THERAPY RESEARCH & DEVELOPMENT

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CHAPTER 1. OVERVIEW

THE GLOBAL GENE AND CELL THERAPY MARKET ACCOUNTED FOR $584 MILLION IN 2016

1.1 BACKGROUND

Gene therapy is the transfer of genetically modified materials into a patient's tissues or cells with the goal of correcting the abnormal genes responsible for a particular disease. The crucial advantage of gene therapy is its capability to provide a durable and possibly curative clinical benefit with a single treatment. Gene therapy may be achieved by administering the gene-delivery vector either directly into the patient (*in vivo*) or into cultured cells that are taken from the patient and then transplanted back (*ex vivo*)[1]. Currently, the most widely used gene-delivery vectors for *in vivo* administration of gene therapy products are virus-based (e.g., adeno-associated viral vectors), but nonviral methods such as cationic liposomes, polymer-based systems, and nanoparticles have also been explored[2].

Originally envisioned for the treatment of monogenic genetic disorders such as hemophilia, gene therapy has been expanded quickly to a diverse range of polygenic genetic diseases including cancers, neurodegenerative diseases, ophthalmic diseases, vascular diseases, etc[1]. The first clinical trial of gene therapy began in the early 1990s and involved viral delivery of genetic material for treatment of adenine deaminase deficiency, an inherited disorder that damages the immune system and leads to severe immune deficiency.

However, several unsuccessful clinical trials slowed the pace of clinical investigations in the late 1990s and early 2000s. Thanks to more basic research related to gene therapy and significant improvements in safety and efficiency of gene delivery methods, a resurgence of clinical studies involving gene therapy has occurred during the last decade. Even more encouraging is the fact that multiple gene therapy products have been approved by drug administration authorities around the world, including the first U.S. Food and Drug Administration (FDA) approval in 2017 of an *in vivo* gene therapy product, Luxturna™, for the treatment of an inherited retinal disease caused by mutation of the RPE65 gene[3]. Currently, there are thousands of gene therapy-related clinical trials that have been completed, ongoing or approved worldwide[1,4].

Cell therapy is the transplantation or injection into patients of either normal or bioengineered human cells for the purpose of restoring the function of diseased cells/tissues or enhancing the ability of immune cells to combat a particular disease. Early research and development (R&D) in this field focused on blood transfusions and bone marrow transplants, whereas more recent R&D has expanded to include therapies involving other types of stem cells as well as engineered immune cells. Stem cell therapy replaces and repairs damaged cells by stem cell transplantation, thereby restoring healthy tissue functions. Stem cell therapy has been

used to treat blood-related diseases (e.g. leukemia), diseases of the nervous system (e.g. Parkinson's disease), cardiovascular diseases (e.g. myocardial infarction), liver diseases (e.g. cirrhosis), endocrine diseases (e.g. diabetes), autoimmune diseases, and infectious diseases.

Immune cell-based therapy, as exemplified by chimeric antigen receptor (CAR) T-cell therapy for cancer treatment, is a combination of gene therapy and cell therapy. T-cells are obtained from cancer patients and genetically modified *ex vivo*, equipping them with the ability to attack cancer cells when re-introduced into the patient's body. CAR T-cell therapy boosts the ability of cancer patients' own immune systems to fight against cancer cells. The early clinical success of this new treatment option has generated a great deal of excitement, leading to enhanced R&D investment and US FDA approval in 2017 of two such therapy agents, Tisagenlecleucel (KYMRIAH®) and Axicabtagene ciloleucel (YESCARTA®)[5,6].

With increasing focus on gene and cell therapies over the past few years, the paces of clinical transformation and commercial development are accelerating rapidly. According to a report published by Allied Market Research[7], the global gene and cell therapy market accounted for $584 million in 2016, and is estimated to reach $4.4 billion by 2023, reflecting a compound annual growth rate of 33.3% from 2017 to 2023. North America was the largest contributor to the market in 2016; however, the Asia-Pacific region is expected to reach the highest growth rate during the forecast period[8].

In an effort to gain better insight into R&D trends in the gene and cell therapy area, the National Science Library of the Chinese Academy of Sciences (NSL), under the guidance of the Development Planning Bureau of the Chinese Academy of Sciences and Chemical Abstracts Service (CAS), a division of the American Chemical Society (ACS), conducted a collaborative data analysis of this area using advanced analysis and visualization tools. The analysis was based on a dataset on gene and cell therapy and related data provided by CAS. This dataset was built from the document database containing patents from 63 patent offices and papers from scientific journals, books, dissertations, meeting proceedings and other related disclosures, compiled worldwide since the early 19th century. It also contained substances in the gene and cell therapy area extracted from CAS's substance collection, which contains over 200 million substances, including over 71 million sequences. The goals of this work were to investigate the overall landscape and trends in the R&D of gene and cell therapies over the past decades and to identify information valuable to future R&D. Because gene therapy and cell therapy are often combined, as in the case of CAR-T cell therapy, these two topics are collectively covered in this report which is part of the biologics report series co-published or to be published by CAS and NSL.

1.2 DATA SOURCES AND METHODS

The report is based on the databases created by CAS, which contain information on publication date, area of scientific specialty (section), nation or region of origin, institution, specific topic (concept) indexing, and various other substance-related indexing data. These data were used to analyze worldwide papers, patents, and registered entities pertaining to R&D in gene and cell therapies. Reported data were mined from about 238,000 published research papers and patents from 1988-2017 in addition to about 6,000 registered entities extracted from the CAS substance collection (Registry℠) in the field of gene and cell therapies. Because this report covers such a broad span of time, the analysis results are organized into five-year periods to facilitate visualization and comparison.

CHAPTER 2. TREND ANALYSIS OF GLOBAL RESEARCH AND DEVELOPMENT IN GENE AND CELL THERAPIES

2.1 GLOBAL TRENDS OF PAPERS AND PATENTS RELATED TO GENE AND CELL THERAPIES

The global trends related to paper and patent publication numbers are shown in Figure 1. From 1988 to 2017, there were 120,664 published papers and 113,229 patent applications associated with 37,724 patent families. Since the 1993-1997 period, the numbers of both papers and patents increased rapidly, and these continued to increase through the period of 2013-2017. The increase in patents related to gene and cell therapies has been especially dramatic in recent years.

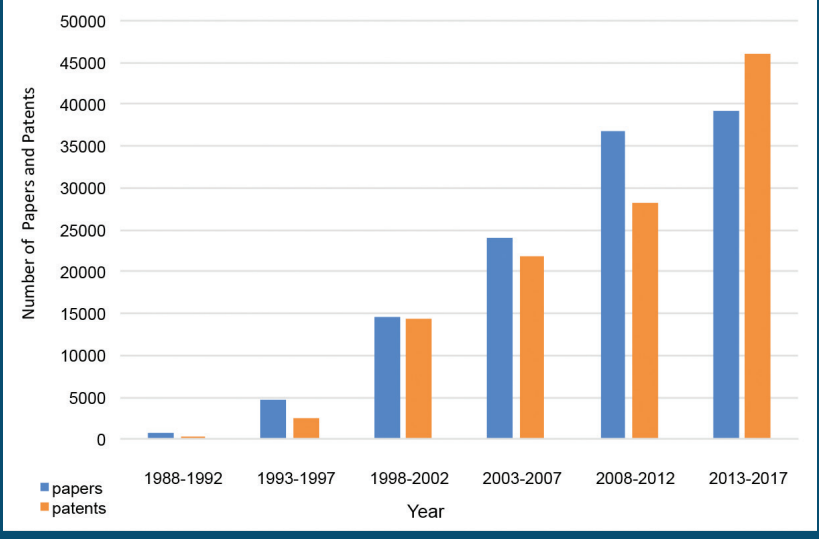


Figure 1. Papers and Patents Related to Gene and Cell Therapies

2.2 SECTION/SPECIALTY DISTRIBUTION OF GENE AND CELL THERAPY RESEARCH

Analysis of gene and cell therapy studies based on area of scientific specialty was conducted using section information provided by CAS. In general, the section specialties of papers and patents included Pharmacology, Immunochemistry, Mammalian Pathological Biochemistry, Biochemical Genetics, Pharmaceuticals, Mammalian Hormones, Mammalian Biochemistry, Microbial, Algal, and Fungal Biochemistry, Biochemical Methods, and Radiation Biochemistry (Table 1). The top two section specialties for paper publications were Pharmacology and Immunochemistry, accounting for 45,724 and 28,407 papers, respectively. Analysis of patent distribution by section revealed that Pharmacology and Pharmaceuticals had the largest share of patents, reflected by total numbers of 18,283 and 17,587, respectively.

Table 1. Top Ten Specialty Sections for Papers and Patents Related to Gene and Cell Therapies

Rank	Papers		Patents	
	Sections	Number of papers	Sections	Number of patents
1	Pharmacology	45,724	Pharmacology	18,283
2	Immunochemistry	28,407	Pharmaceuticals	17,587
3	Mammalian Pathological Biochemistry	25,312	Biochemical Genetics	13,647
4	Biochemical Genetics	23,864	Immunochemistry	7,995
5	Pharmaceuticals	21,159	Biochemical Methods	7,600
6	Mammalian Hormones	8,446	Mammalian Biochemistry	7,083
7	Mammalian Biochemistry	7,423	Mammalian Pathological Biochemistry	6,532
8	Microbial, Algal, and Fungal Biochemistry	3,087	General Biochemistry	2,834
9	Biochemical Methods	2,780	Mammalian Hormones	2,441
10	Radiation Biochemistry	1,499	Microbial, Algal, and Fungal Biochemistry	1,992

Analysis of the top 5 specialty sections for papers (Figure 2) demonstrated that the total number of papers published in Pharmacology, Immunochemistry, Mammalian Pathological Biochemistry and Pharmaceuticals continued to increase for every 5-year period up until 2012. The slight decrease during the 2013-2017 time period may reflect the fact that R&D was becoming more diversified, involving specialty areas (sections) of interest in addition to the five listed in Figure 2, since the total number of paper publications was actually highest during this time period (Figure 1).

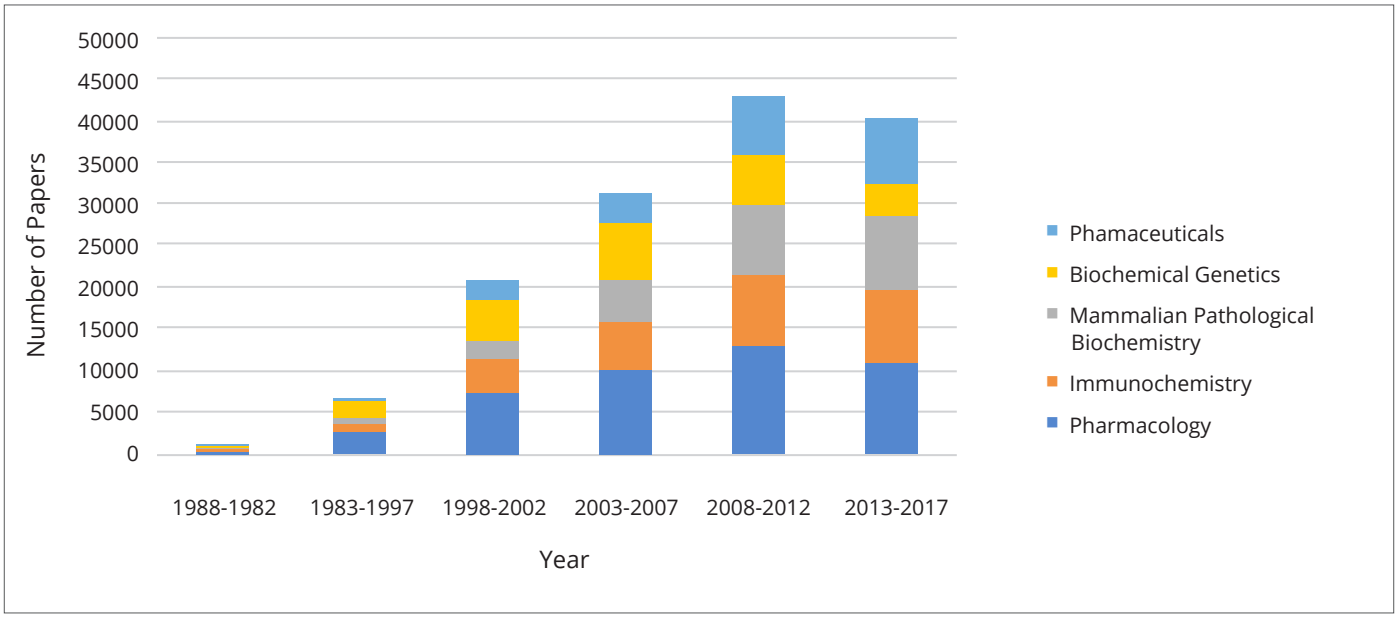


Figure 2. Top Five Specialty Sections of Papers on Gene and Cell Therapies

Analysis of the top five sections for patents (Figure 3) showed that there were very few gene and cell therapy-related patent applications prior to 1998. However, subsequent to the 1998-2002 period, the numbers of patent applications in all five sections grew significantly, especially in the Pharmaceuticals section, where the number of patents reached 1,446 during the 2013-2017 time period.

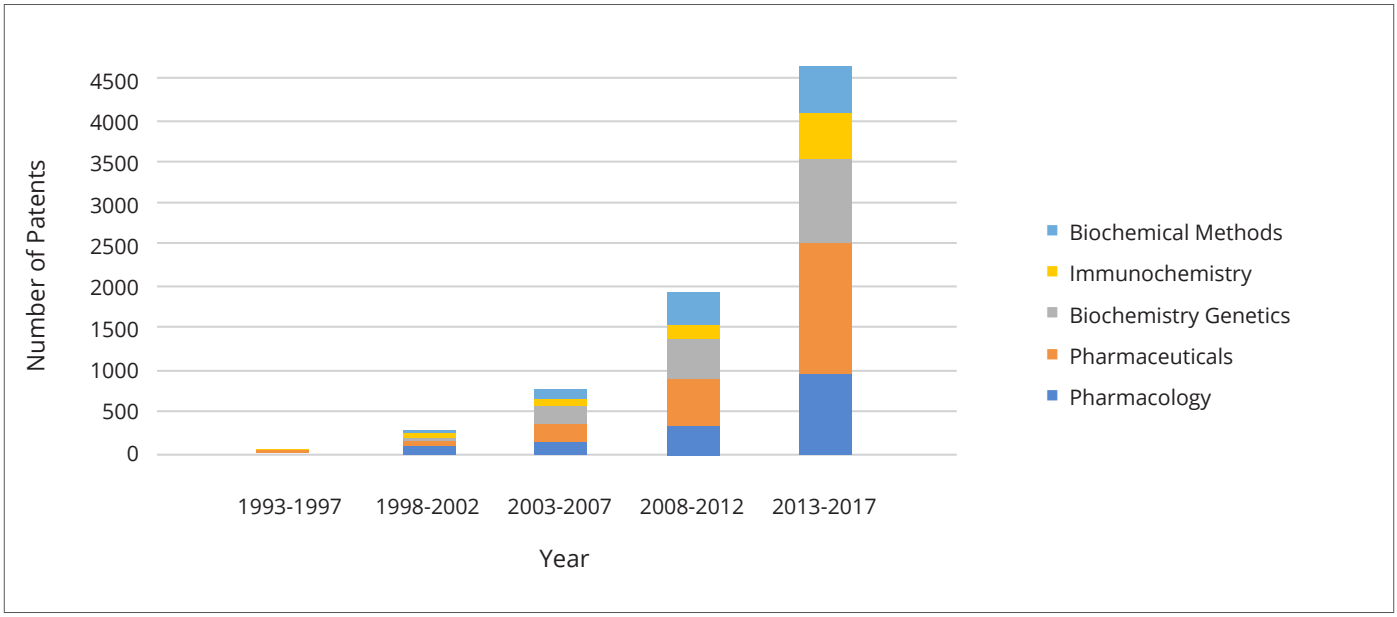


Figure 3. Top Five Specialty Sections of Patents Related to Gene and Cell Therapies

2.3 DISTRIBUTION AND EVOLUTION OF RESEARCH TOPICS ON GENE AND CELL THERAPIES

Indexed concepts provided by CAS were used to cluster papers and patents related to gene and cell therapies over the 30-year time frame from 1988 to 2017. The data were grouped into 5-year time frames in order to reveal changes in research topics over time.

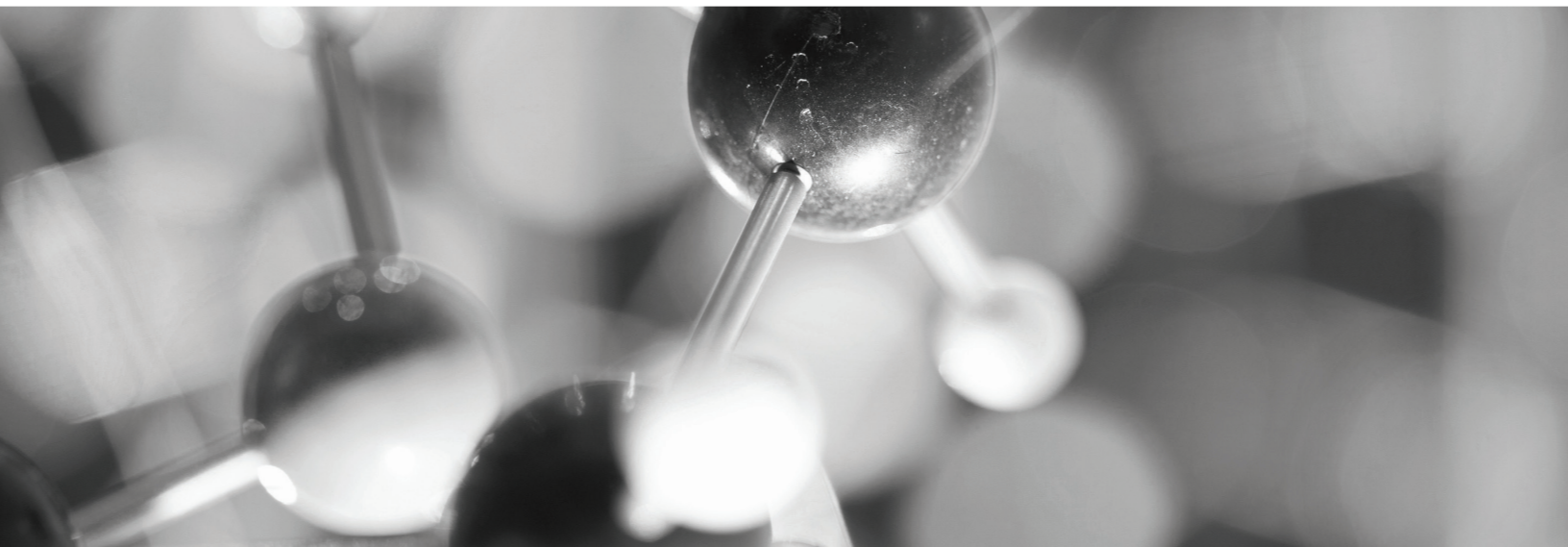
As shown in Figure 4, during 1988 to 1992, the primary research topics centered on development of anti-tumor drugs (green dots), genetic transformation technology (red dots), cell transplantation (yellow dots), and immune system factors such as T-cells, NK cells and antibodies (blue dots).

While most research continued to focus on cancer treatment during 1993-1997, studies on the role of various viral vectors also emerged (red dots). In addition, research on tumor suppressor genes such as p53 began to attract researchers' attention (red dots). R&D on interleukins, CD4 T-cells, CD8 T-cells and bone marrow transplantation (green dots) and AIDS treatment (blue dots) also gradually increased.

During 1998-2002, additional effort was devoted to anti-tumor therapies and associated topics including apoptosis, hematopoietic precursor cells, stem cells (red dots), as well as soluble tumor necrosis factor (green dots). Meanwhile, antibodies, protein sequencing, molecular cloning, and drug screening studies also received a fair amount of attention (blue dots).

The two major areas of research during 2003 to 2007 were related to anti-tumor agents (red dots) and stem cells (green dots). In particular, there was an increased effort toward improving drug delivery methods for anti-tumor agents. Meanwhile, studies on adenoviral vectors, hematopoietic precursor cells, and cell transplantation also increased significantly. In addition, research involving immunology topics, such as T-cells and interleukins (yellow dots), was expanding. Technology-related research publications (blue dots), with a major emphasis on molecular cloning and antibody production, were also rising rapidly in numbers.

From 2008 to 2012, research efforts on stem cells, cell proliferation (red dots), and stem cell transplantation (yellow dots) intensified. This may be partly related to the high interest in the first non-hematopoietic stem cell-based drug, Prochymal, for the treatment of acute graft-vs-host disease (GvHD). Meanwhile, a broad range of protein CD antigens including CD3, CD4, CD19 and CD14 were also under intensive investigation, perhaps as a result of an increased interest in CAR T-cell therapy prompted by the successful outcomes of the first CAR T-cell clinical trial in 2008. The number of studies related to drug targets, probiotics and tumors was expanding due to an increased interest in these areas as well.



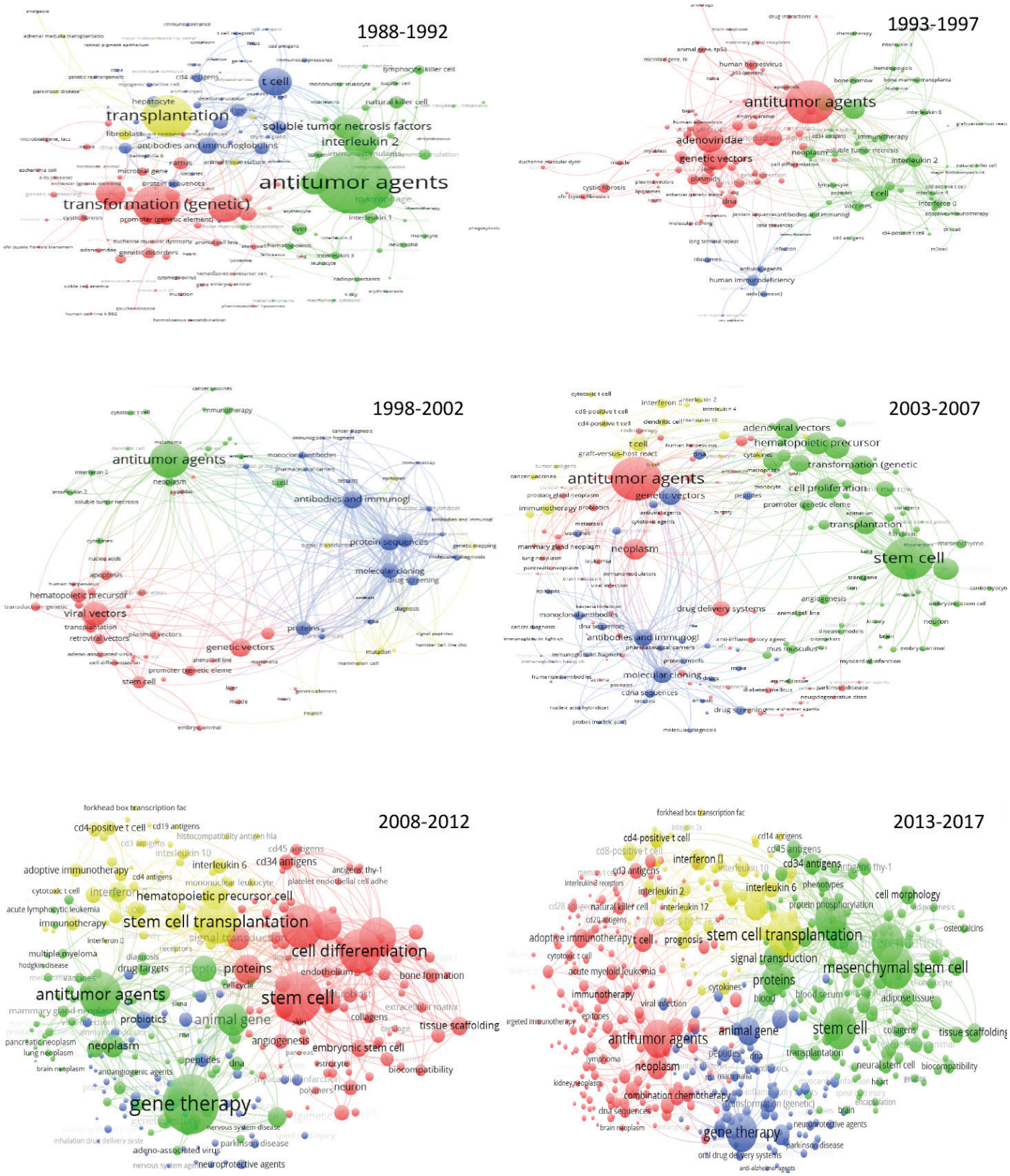


Figure 4. Research Topic Distribution from 1988 to 2017

Stem cells (green dots) and stem cell transplantation (yellow dots) were major research topics from 2013-2017. Additional basic research on signal transduction (green dots) and further studies on protein targets such as CD8, CD20, CD28, CD30, CD34, and CD45 were notable during this time period. There was an enhanced interest in the relationships between probiotics and tumors (blue dots). Studies on various vectors, antibody preparation techniques, T-cells, and NK cells continued to be popular (red dots). New approaches to therapy represented by genomic editing techniques such as CRISPR (clustered regularly interspaced short palindromic repeats) were also beginning to receive attention.

2.4 DISTRIBUTION OF GLOBAL R&D IN MAJOR COUNTRIES/REGIONS

2.4.1 DISTRIBUTION IN MAJOR COUNTRIES/REGIONS

Since 1988, the top five countries producing research papers on gene and cell therapies were the United States, China, Japan, Germany, and the United Kingdom (Figure 5). These five countries together accounted for 70% of the total papers in the world. Although nearly 80 countries or regions around the world applied for patents related to gene and cell therapies during this period, the top five countries in terms of patent applications were the United States, China, Japan, South Korea and Germany, together accounting for 68% of the total number of patent applications in the world. The US has been holding the predominant leadership position, generating far more papers and patents than any other country. China ranked second in terms of both paper and patent publications.

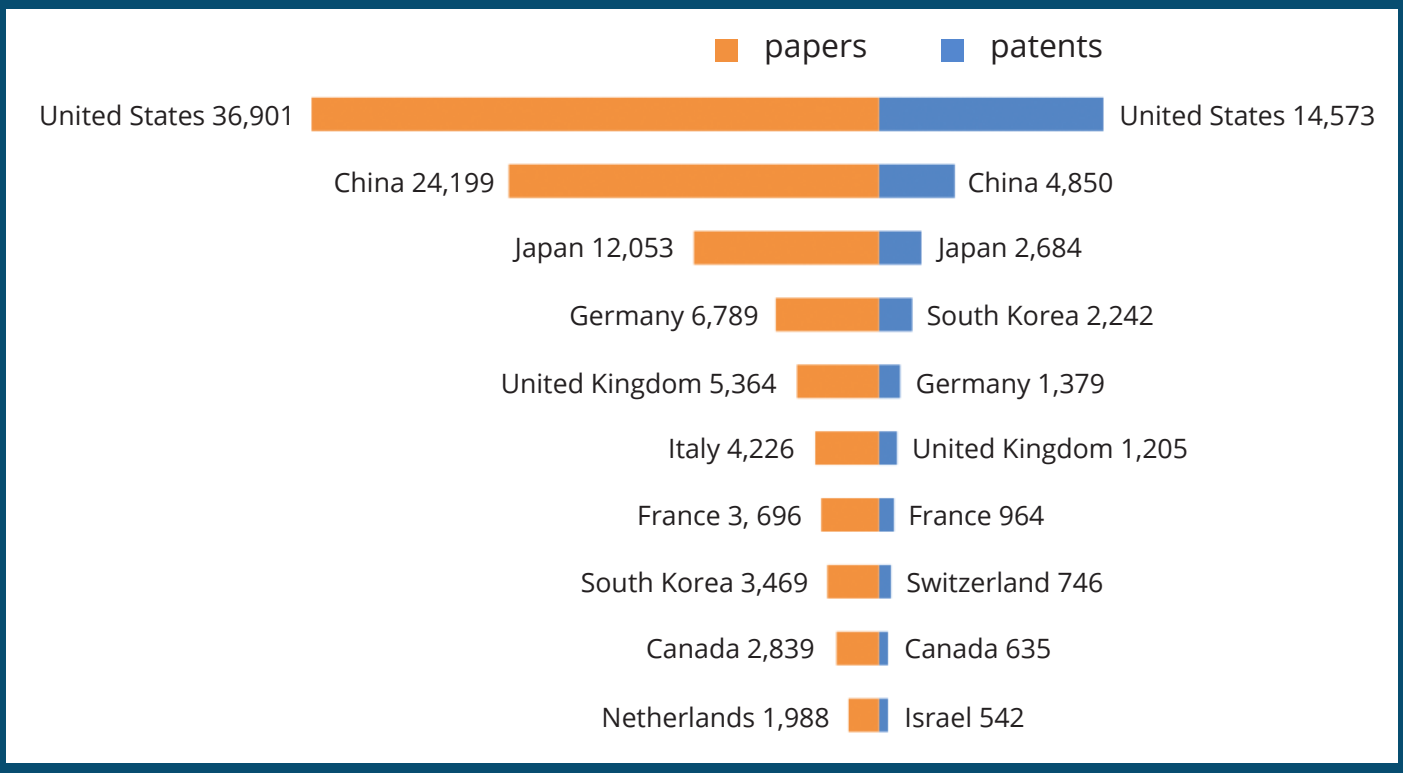


Figure 5. Patents and Papers Related to Gene and Cell Therapies by Country/Region

2.4.2 CHANGES IN COUNTRY/REGION DISTRIBUTION OVER TIME

Analysis of the paper publications related to gene and cell therapies for the 1988-2017 period (Figure 6) indicates that the United States demonstrated steady growth and has continuously been in the leading position throughout the entire period. China's paper publication numbers were much lower than those of the other four countries prior to 1997. However, those numbers increased rapidly starting with the 2003-2007 period and have since surpassed those of Japan, Germany and the United Kingdom, placing China in second place in terms of publication numbers over the last 15 years. In contrast, Japan, Germany and the United Kingdom showed only modest, if any, growth during this period.

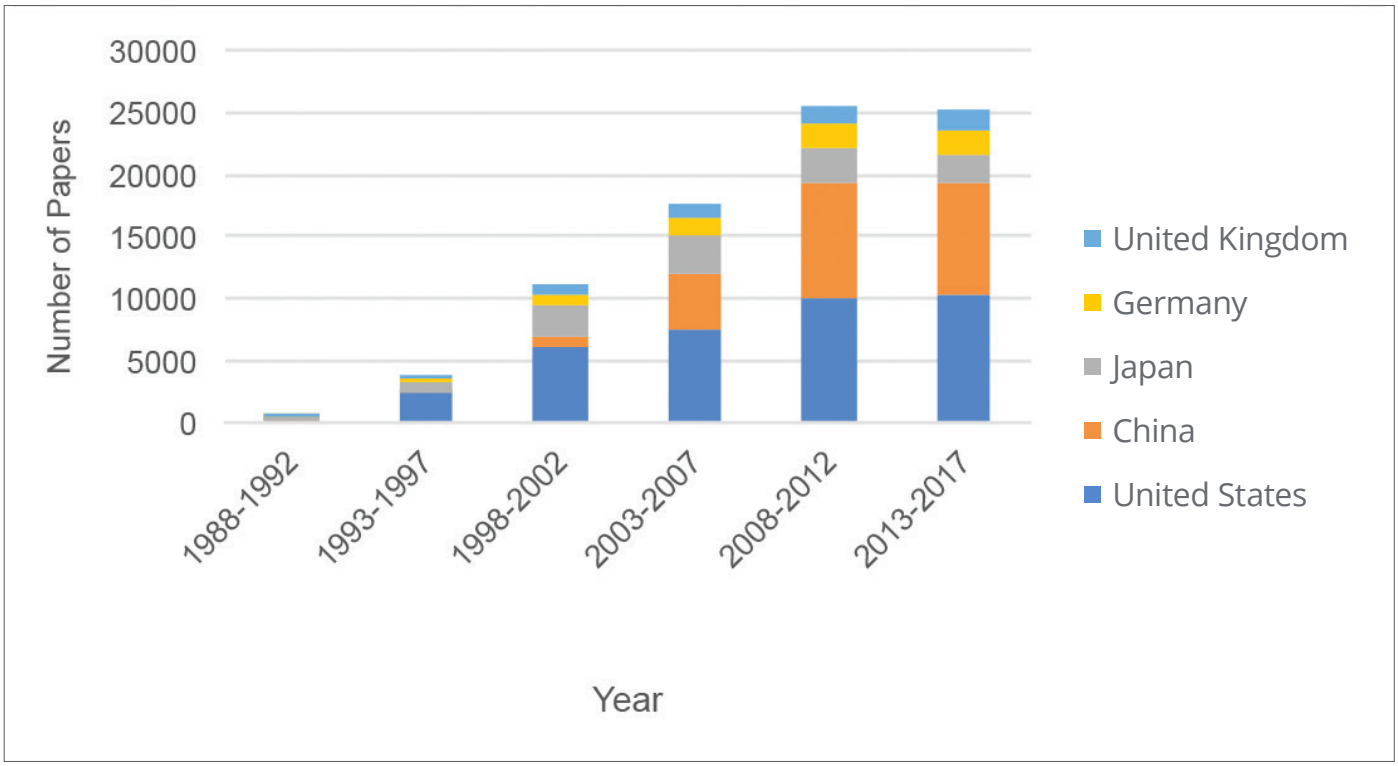


Figure 6. Papers Related to Gene and Cell Therapies Published by Top 5 Countries over Time

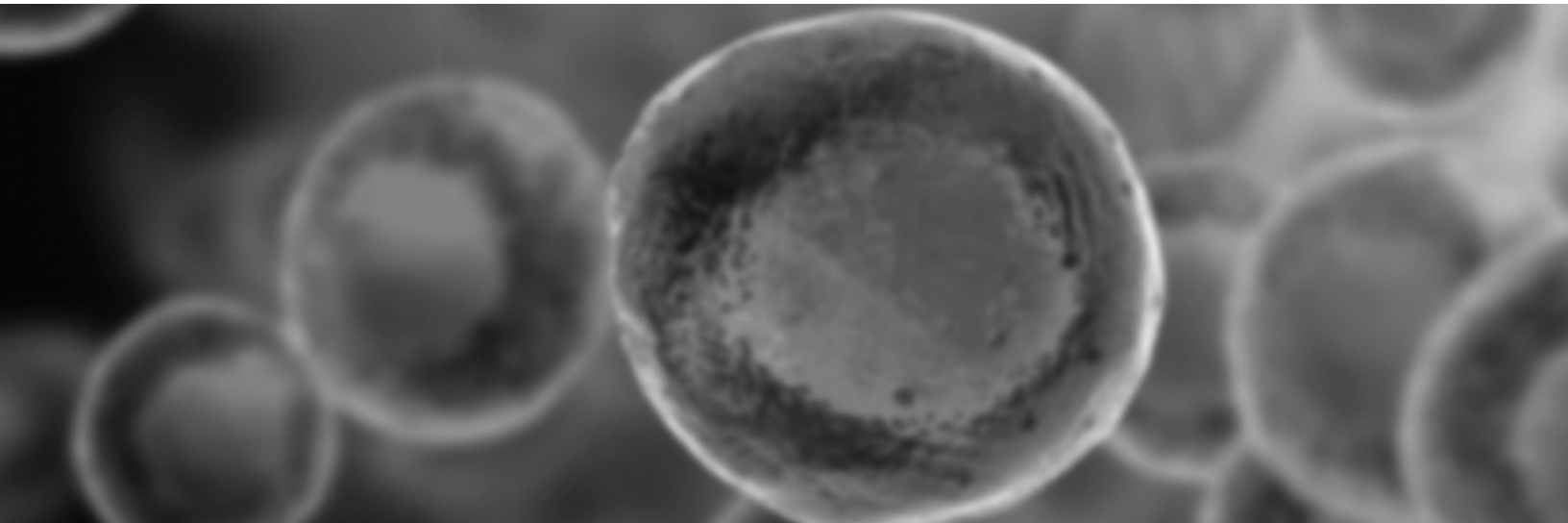


Figure 7 shows that the top five countries leading in patent applications during the entire 1988-2017 time frame were the United States, China, Japan, South Korea, and Germany. The US held a dominant role throughout the entire period with 4,746 patent applications during 2013-2017. Although China lagged early on, it quickly caught up during the 2008-2012 time period, and since then, the number of patent applications from China has indeed exceeded the combined total from Japan, South Korea, and Germany.

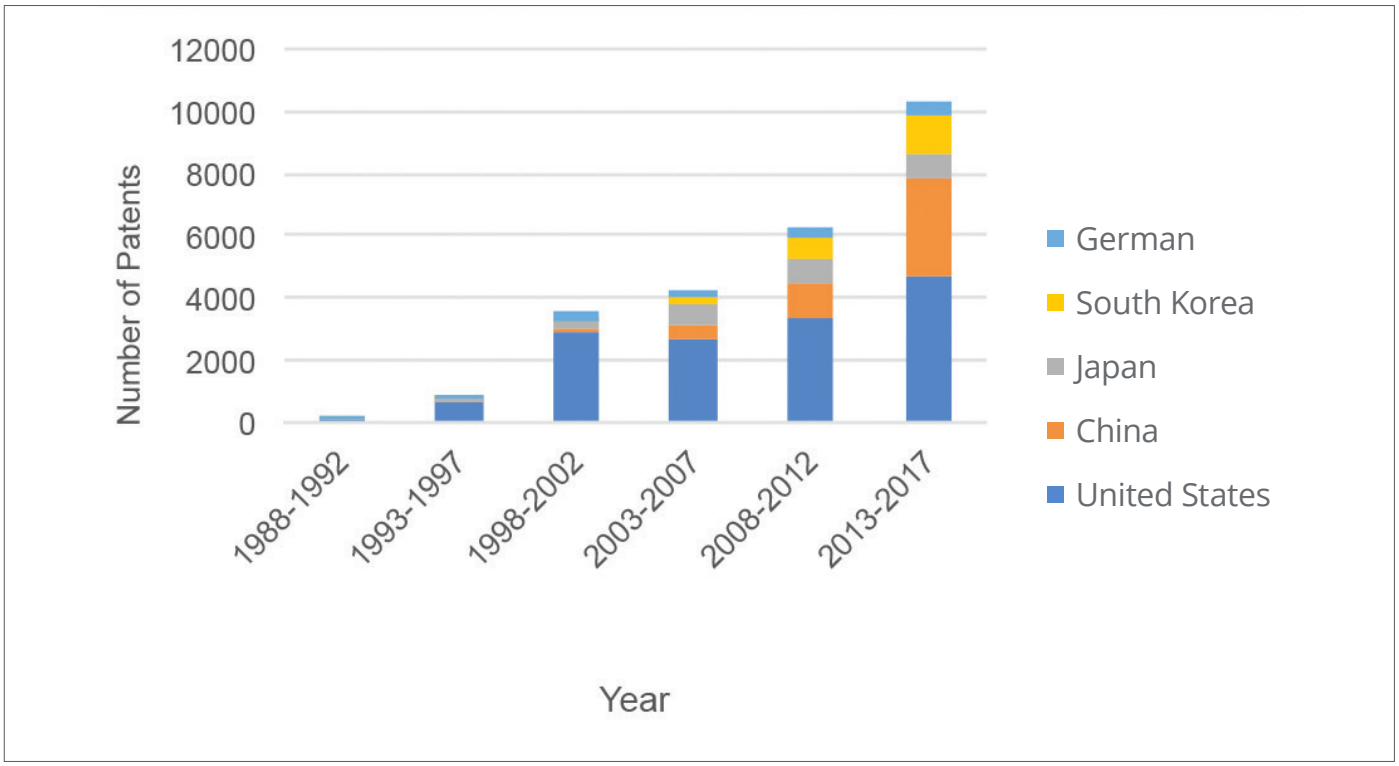
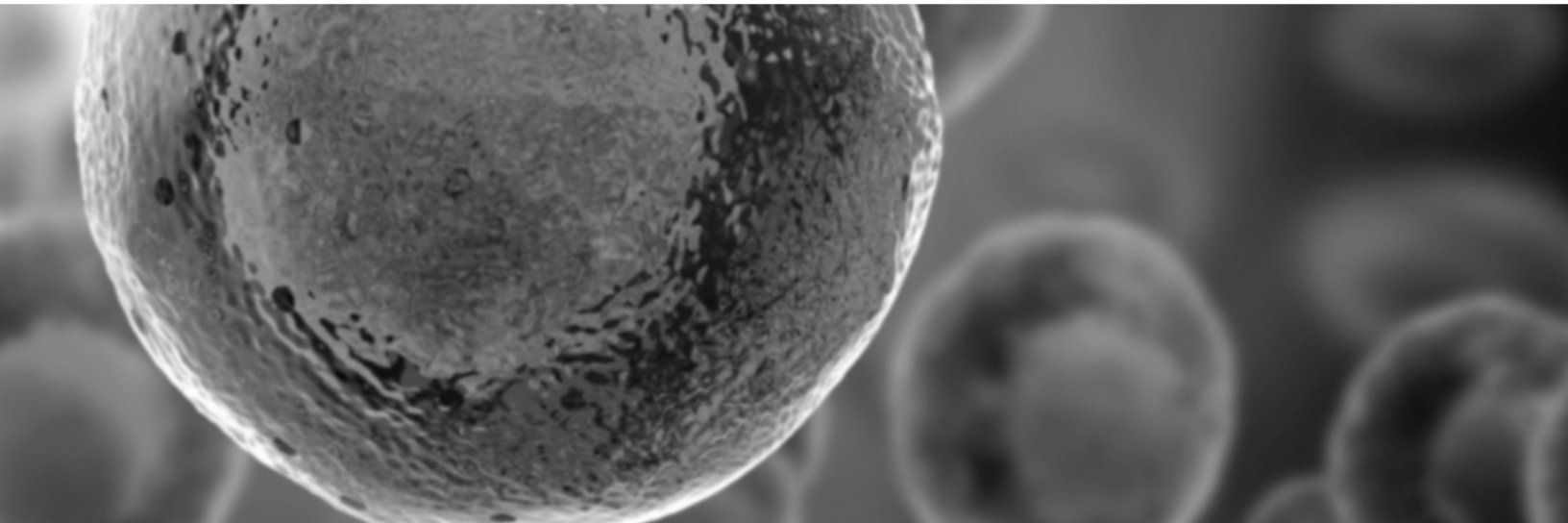


Figure 7. Patent Applications Related to Gene and Cell Therapy by Top 5 Countries over Time



2.4.3 FLOW OF PATENT APPLICATIONS BETWEEN MAJOR COUNTRIES/REGIONS

The flow of patents between countries refers to patents having inventors from one country that submit their patent applications to a different country's patent office. Figure 8 shows the flow of gene and cell therapy-related patent applications among the top five patenting countries: the United States, China, Japan, South Korea, and Germany. The United States, Japan, and Germany all attached great importance to applying for patents in other countries, likely for protection and commercialization of patented technologies in other countries. The United States has protected its intellectual property heavily in the Japanese, Chinese, and Korean markets with 2,702, 1,512 and 993 patents, respectively, in those countries. Japan, Germany and South Korea all focused more on patenting their technologies in the US market and applied for 1,136, 751 and 476 patents, respectively, in the US. Although China had a large number of patent applications, it only applied for 155, 47 and 18, respectively, in the United States, Japan, and South Korea, and only a single patent application in Germany. While South Korea has received more patent applications from the US, Japan, and Germany, it has applied for more patents in China than China has applied for in South Korea.

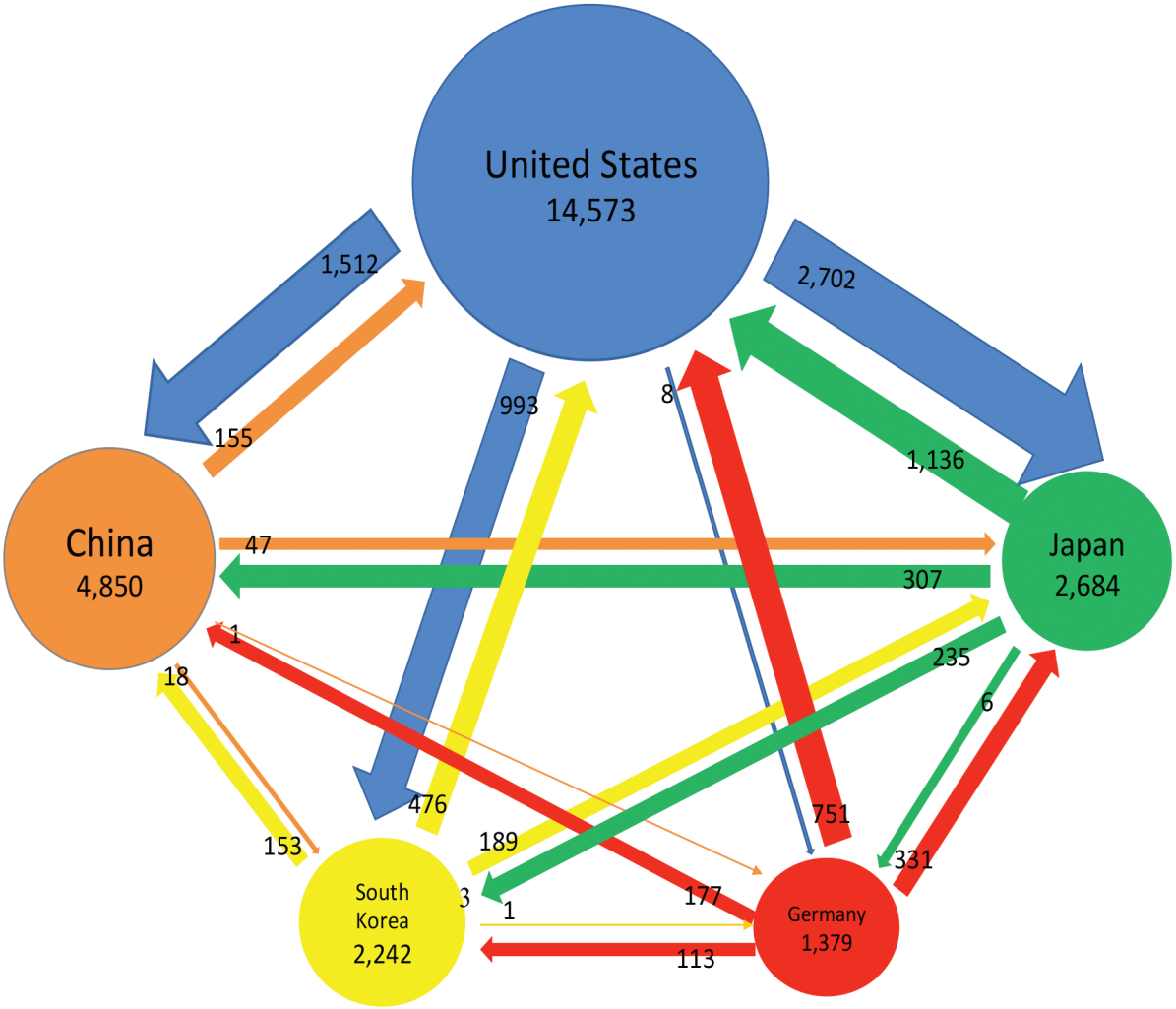


Figure 8. International Flow of Patent Technologies for Therapeutic Fusion Proteins (Note: The width of the arrow is positively correlated with the proportion of patent applications.)

2.5 PAPERS AND PATENTS WITH RELATIVELY HIGH IMPACT IN THE FIELD OF GENE AND CELL THERAPIES

In order to identify high-impact papers related to gene and cell therapies published after 2000, an analysis of the citation numbers for individual papers and impact factors for journals was performed. In the event of two papers having similar citation numbers and impact factors, the more recently published paper was weighed more in the analysis. The high ranking documents were then reviewed by CAS's experts.

Table 2 indicates that papers having the highest level of impact were mainly focused on 1) treatments for diseases including SCID, cancer, and hemophilia, 2) the use of stem cells to aid in regeneration, and 3) the development of gene editing and delivery methods. In particular, the top three papers related to the CRISPR/Cas systems have significantly impacted the field of gene and cell therapies. Also, CAR T-cell immunotherapy has become an emerging topic in recent years. The use of stem cells in regeneration, although not a new topic, is still attracting much attention as shown by the fact that close to half of the high-impact papers relate to stem cell therapies.

Table 2. High-Impact Papers Related to Gene and Cell Therapies from 2000-2017

No.	Title	Source
1	Multiplex genome engineering using CRISPR/Cas systems	Science (Washington, DC, United States) (2013), 339(6121), 819-823
2	A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity	Science (Washington, DC, United States) (2012), 337(6096), 816-821
3	RNA-guided human genome engineering via Cas9	Science (Washington, DC, United States) (2013), 339(6121), 823-826
4	LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1	Science (Washington, DC, United States) (2003), 302(5644), 415-419
5	Sipuleucel-T immunotherapy for castration-resistant prostate cancer	New England Journal of Medicine (2010), 363(5), 411-422
6	Design and development of polymers for gene delivery	Nature Reviews Drug Discovery (2005), 4(7), 581-593
7	Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease	Science (Washington, D. C.) (2000), 288(5466), 669-672
8	Nonviral vectors for gene delivery	Chemical Reviews (Washington, DC, United States) (2009), 109(2), 259-302
9	Cancer regression in patients after transfer of genetically engineered lymphocytes	Science (Washington, DC, United States) (2006), 314(5796), 126-129
10	Progress and problems with the use of viral vectors for gene therapy	Nature Reviews Genetics (2003), 4(5), 346-358
11	Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia	New England Journal of Medicine (2011), 365(8), 725-733
12	Cellular and molecular regulation of muscle regeneration	Physiological Reviews (2004), 84(1), 209-238
13	Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study	Lancet (2008), 371(9624), 1579-1586
14	Generation of a functional mammary gland from a single stem cell	Nature (London, United Kingdom) (2006), 439(7072), 84-88
15	Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response	Nature Medicine (New York, NY, United States) (2006), 12(3), 342-347
16	Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts	Nature Biotechnology (2007), 25(9), 1015-1024
17	Safety and efficacy of gene transfer for Leber's congenital amaurosis	New England Journal of Medicine (2008), 358(21), 2240-2248
18	Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells	Nature Biotechnology (2006), 24(11), 1392-1401
19	DNA vaccines: Immunology, application, and optimization	Annual Review of Immunology (2000), 18, 927-974
20	Chimeric antigen receptor-modified T cells for acute lymphoid leukemia	New England Journal of Medicine (2013), 368(16), 1509-1518
21	piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells	Nature (London, United Kingdom) (2009), 458(7239), 766-770
22	Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease	Nature (London, United Kingdom) (2002), 418(6893), 50-56

No.	Title	Source
23	Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets	Science (Washington, DC, United States) (2001), 292(5520), 1389-1394
24	Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration	Nature Medicine (New York, NY, United States) (2003), 9(6), 702-712
25	Regulatory T cells in transplantation tolerance	Nature Reviews Immunology (2003), 3(3), 199-210
26	A controlled trial of intratumoral ONYX-015, selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer	Nature Medicine (New York) (2000), 6(8), 879-885
27	Viral vectors for gene therapy: the art of turning infectious agents into vehicles of therapeutics	Nature Medicine (New York) (2001), 7(1), 33-40
28	Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning	Science (Washington, DC, United States) (2002), 296(5577), 2410-2413
29	High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma	New England Journal of Medicine (2003), 348(19), 1875-1883
30	Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy	Science (Washington, DC, United States) (2009), 326(5954), 818-823

High-impact patents were identified by citation numbers and numbers of patent offices they were filed with (Table 3). As shown in the table, CAR T-cell therapies, gene editing technologies, and stem cell therapies were the three areas of focus in patent applications.

Table 3. High-Impact Patents Related to Gene and Cell Therapies from 2000-2017

No.	Year	Title	Organization
1	2017	Treatment of intervertebral disc degeneration using human umbilical cord tissue-derived cells	Depuy Synthes Products, Inc., USA
2	2013	Variants of CRISPR endonucleases regulated by small molecules and their uses	University of California, USA
3	2015	Computer-based systems for modeling CRISPR-Cas systems in the design and selection of target sequences and guide RNAs	The Broad Institute Inc., USA; Massachusetts Institute of Technology
4	2015	Regeneration and repair of neural tissue following injury	DePuy Synthes Products, Inc., USA
5	2015	Bone-derived porous structures for the delivery of cells and therapeutics	The Invention Science Fund I, LLC, USA
6	2013	Bispecific chimeric antigen receptors for immunotherapy	Seattle Children's Research Institute, USA
7	2008	Culture and differentiation of CNS-derived multipotent mammalian neural stem cell, and use for drug screening and treatment of neurodegenerative diseases	Neurospheres Holdings Ltd., CAN.
8	2010	Methods of using regenerative cells in the treatment of musculoskeletal disorders	Cytori Therapeutics, Inc., USA
9	2014	Preparation of chimeric antigen receptor comprising binding pair, modulatory domain, dimerization pair, transmembrane domain and intracellular signaling domain for cancer therapy	University of California, USA
10	2014	CAS-CRISPR editing of T cell genomes for immunotherapy	Cellectis, France
11	2013	Modified polynucleotides for production of biologics and proteins associated with human disease, pharmaceutical compositions containing them, and methods for preparation, administration and expression in mammals	Moderna Therapeutics, USA

No.	Year	Title	Organization
12	2013	Compositions comprising nanostructures for cell, tissue and artificial organ growth, and methods for making and using same	The Regents of the University of California, USA
13	2014	Preparation of multi-chain chimeric antigen receptor to redirect immune cell's target specificity and reactivity for adoptive immunotherapy of cancer and viral infection	Cellectis, France
14	2013	MAPC generation of lung tissue	University of Minnesota, USA
15	2013	Use of microbial CRISPR defensive systems in the development of ribonucleoproteins for nucleic acid manipulation	Wageningen Universiteit, Netherland
16	2013	CAR-positive T cells genetically modified to eliminate expression of T- cell receptor and/or HLA	University of Texas System, USA
17	2013	Chimeric antigen receptors targeting B-cell maturation antigen for the treatment of multiple myeloma	United States Dept. of Health and Human Services, USA
18	2015	Tumor antigen-specific chimeric antigen receptors and CAR-modified T cells for cancer therapy	Novartis AG, Switz.; The Trustees of University of Pennsylvania
19	2014	Oncolytic virus encoding PD-1 binding agents and uses of the same	Morningside Technology Ventures Ltd., Monaco
20	2016	Engineered immune cells expressing target antigen-binding chimeric antigen receptor for adoptive cell therapy of cancer or infection	Juno Therapeutics, Inc., USA

2.6 RESEARCH ORGANIZATIONS CONDUCTING GENE AND CELL THERAPY R&D

2.6.1 MAJOR RESEARCH PAPER-PUBLISHING ORGANIZATIONS

Among the top 20 organizations worldwide, based on total number of paper publications related to gene and cell therapies, 12 are located in the United States, 5 in China, and 3 in Japan (Table 4). These top 20 organizations are mostly of universities and research institutes. The top 5 organizations are, in order, the University of California, the University of Texas, the National Institutes of Health, the University of Pennsylvania, and the University of Pittsburgh. The University of California alone produced 1,940 papers. The organizations ranking 6th to 10th in terms of publication numbers were Harvard University, Shanghai Jiao Tong University, Huazhong University of Science and Technology, Osaka University and the University of Michigan. The Mayo Clinic and Peking University also published a relatively high number of papers over the past three years (2015-2018). Additional data on organizations publishing papers on gene and cell therapies are provided in Appendix I.

Table 4. Top 20 Organizations Based on Total Number of Papers on Gene and Cell Therapies

Rank	Organization	Country	Organization Type	Number of Papers	Time period	% in Most Recent 3 Years
1	University of California	USA	University	1,940	1970 -2018	16.91%
2	University of Texas System	USA	University	1,598	1976 -2018	17.21%
3	National Institutes of Health (USA).	USA	Corporation	1,272	1986 - 2018	13.6%
4	University of Pennsylvania	USA	University	987	1990 - 2018	17.53%
5	University of Pittsburgh	USA	University	905	1991 - 2018	9.39%
6	Harvard University	USA	University	798	1989 - 2018	15.41%
7	Shanghai Jiao Tong University	China	University	795	1992 - 2018	18.49%
8	Huazhong University of Science and Technology	China	University	757	1997 - 2018	9.11%
9	Osaka University	Japn	University	753	1985 - 2018	6.51%
10	University of Michigan	USA	University	749	1981 - 2018	13.22%
11	Stanford University	USA	University	725	1971 - 2018	18.21%
12	Sun Yat-sen University	China	University	711	1999 - 2018	13.64%
13	Kyoto University	Japan	University	698	1980 - 2018	10.6%
14	Johns Hopkins University	USA	University	696	1982 - 2018	14.37%
15	University of Washington	USA	University	691	1986 - 2018	14.47%
16	Mayo Clinic	USA	Research Institute	686	1985 - 2018	21.75%
17	University of Tokyo	Japan	University	672	1978 - 2018	11.76%
18	Baylor College of Medicine	USA	Corporation	670	1984 - 2018	8.36%
19	Peking University	China	University	656	2000 - 2018	20.43%
20	Sichuan University	China	University	630	1999 - 2018	17.14%

2.6.2 MAJOR ORGANIZATIONS BASED ON PATENT APPLICATIONS

Among the top 20 organizations filing patent applications related to gene and cell therapies, 10 are from the United States, 3 from Switzerland, 2 each from China and France, and 1 each from the United Kingdom, Japan and South Korea (Table 5).

These top 20 organizations consist of 9 universities, 6 corporations and 5 research institutes. The top 5 applicants were GlaxoSmithKline, the University of California, the US Department of Health and Human Services, the University of Texas, and Novartis. Among them, GlaxoSmithKline had the largest number of patent applications. Additional data on organizations publishing patents related to gene and cell therapies is in Appendix II.

Table 5. Top 20 Organizations Worldwide Based on Patent Applications Related to Gene and Cell Therapies

Rank	Organization	Country	Organization Type	Number of Patents	Patent active period	% in Most Last 3 Years
1	GlaxoSmithKline	UK	Corporation	896	1988 - 2018	0.95%
2	University of California	USA	University	565	1983 - 2018	27.3%
3	U.S. Department of Health and Human Services	USA	Research organization	332	1989 - 2018	21.15%
4	University of Texas System	USA	University	304	1991 - 2018	21.05%
5	Novartis AG	Switzerland	Corporation	294	1964 - 2018	25.42%
6	University of Pennsylvania	USA	University	291	1994 - 2018	37.11%
7	Chinese Academy of Sciences	China	Research organization	280	1998 - 2018	45.85%
8	Institut National de la Sante et de la Recherche Medicale	France	Research organi-zation	262	1993 - 2018	43.51%
9	Johns Hopkins University	USA	University	253	1989 - 2018	21.34%
10	Sanofi	France	Corporation	247	1987 - 2017	2.92%
11	Massachusetts General Hospital	USA	Research organization	229	1988 - 2018	19.65%
12	Seoul National University	Korea	University	224	2002 - 2018	32.42%
13	Societe des Produits Nestle S.A.	Switzerland	Corporation	224	2000 - 2017	20.09%
14	Incyte Corp.	USA	Corporation	216	1998 - 2004	0%
15	Harvard University	USA	University	191	1993 - 2018	34.55%
16	Kyoto University	Japan	University	187	2000 - 2018	35.29%
17	Columbia University	USA	University	183	1989 - 2018	23.08%
18	F. Hoffmann-La Roche & Co. AG	Switzerland	Corporation	178	1991 - 2018	15.65%
19	Academy of Military Medical Sciences	China	Research organization	175	2001 - 2017	29.71%
20	Massachusetts Institute of Technology	USA	University	173	1994 - 2018	32.16%

CHAPTER 3. GENE AND CELL THERAPY-RELATED SUBSTANCES

3.1 CHANGES IN THE NUMBER OF GENE AND CELL THERAPY-RELATED SUBSTANCES OVER TIME

The gene and cell therapy-related substances analyzed for this report include CAS-registered agents contained in the CAS substance collection (Registry[SM]) and are either drugs (or potential drugs) or delivery vectors. These substances also include nucleic acid and peptide/protein sequences used in the preparation of gene and cell therapy products. During the last three decades, a total of 5,233 substances related to gene and cell therapies were registered, as shown in Figure 9. Prior to 1997, only a very small number of gene and cell therapy-related substances were registered. However, since 1998, the number of registered substances has gradually increased, reaching 715 in the 2008-2012 period. During the 2013-2017 period, the number of registered substances grew even more dramatically, reaching 2,867, about four times that of the previous five years. An analysis of the gene and cell therapy-related substances registered during the first half of 2018 indicates a total of more than 600 new agents, which is on track to significantly exceed the previous annual average numbers. Based on this trend, it is reasonable to predict that many more therapeutic products related to gene and cell therapies will likely enter clinical trials and be approved in the next few years.

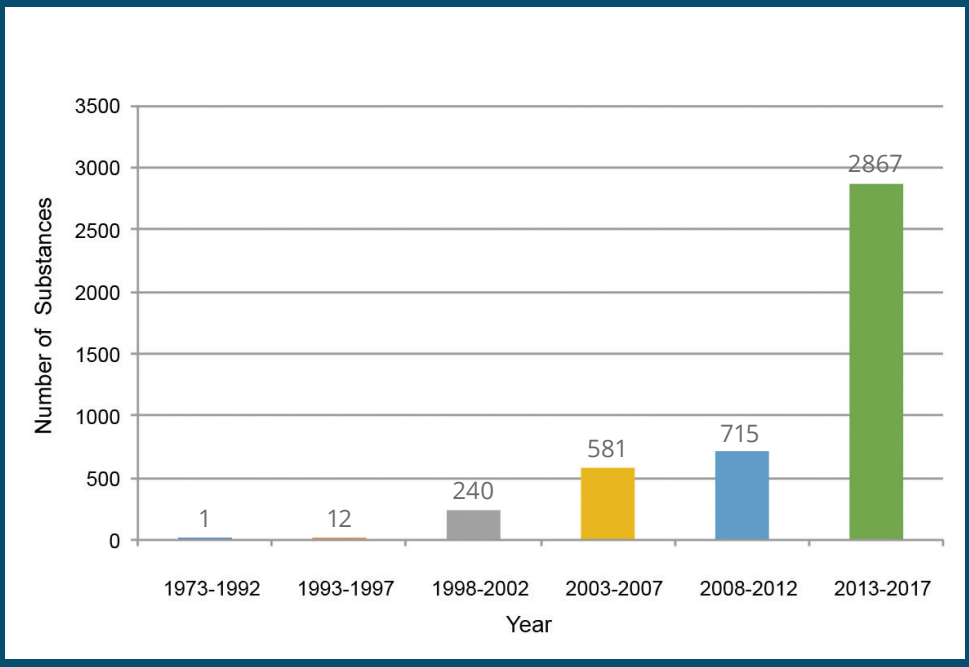


Figure 9. Five-Year Totals of Gene and Cell Therapy-Related Substances (Note: Substances related to gene editing technologies are not included here but shown in Figure 17)

3.2 MAJOR GENE AND CELL THERAPY-RELATED SUBSTANCES

Of the gene and cell therapy-related substances, the substance associated with the largest number of published papers and patents over the past three decades is Picibanil (lyophilized Streptococcus cells with anti-tumor activity) (Figure 10). This is followed by Sipuleucel-T (an autologous prostate cancer therapy vaccine for cellular immunotherapy, which selectively targets the prostate-specific antigen/ prostate acid phosphatase), Talimogene laherparepvec (immunotherapeutic and oncolytic virus), and GVAx (an autologous pancreatic cancer vaccine composed of patient-specific pancreatic cancer cells genetically modified to secrete granulocyte-macrophage colony-stimulating factor in order to boost the patient's immune system). Other than Alipogene tiparvovec, a gene therapy product for treating lipoprotein lipase deficiency, all of the other listed agents are designed for cancer treatment, with two designed for CAR T-cell therapy.

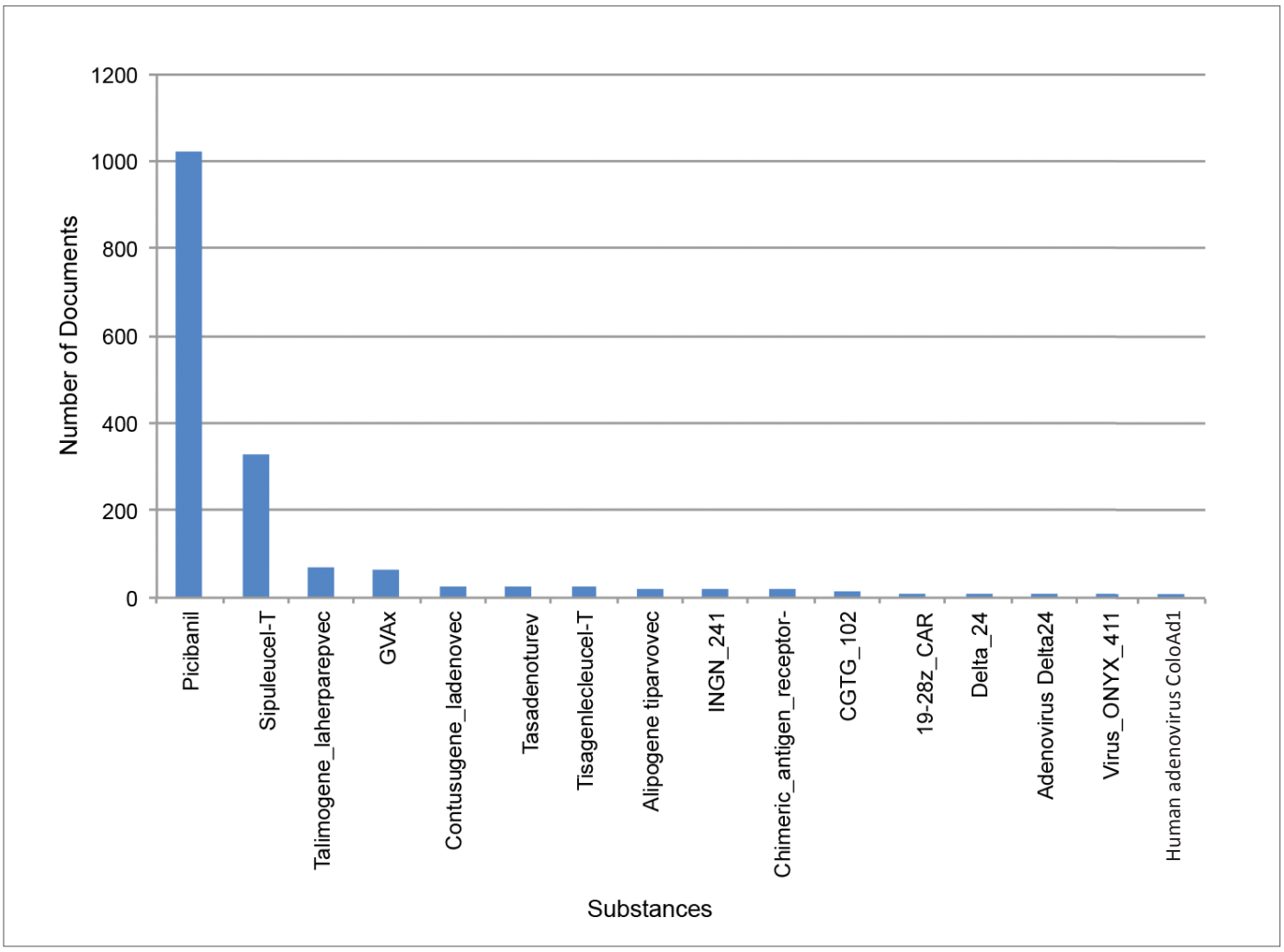


Figure 10. Appearance of Top 15 Gene and Cell Therapy-Related Substances in Papers and Patents

3.3 RELATIONSHIPS BETWEEN GENE AND CELL THERAPY-RELATED SUBSTANCES AND DISEASE CATAGORIES

In order to investigate the use of gene and cell therapy-related substances in the treatment of diseases, the relationships between substances and diseases were analyzed. Figure 11 shows the relationships among the top ten gene and cell therapy-related substances and diseases mentioned in CAS-indexed documents. Overall, most of the substances were studied primarily in relationship to cancers, and were less explored in relation to other types of diseases. Among them, Picibanil and Sipuleucel-T were studied most, whereas Talimogene laherparepvec and GVAx were moderately studied in cancer treatment.

disease / substance	Neoplasm	Digestive system disease	Infection	Lymphatic system disease	Immune disease	Respiratory system disease	Inflammation	Musculoskeletal disease	Hematopoietic disorders	Cardiovascular disease	Mental and behavioral disorders	Endocrine system disease	Degenerative disease	Nervous system disease	Connective tissue disease
Picibanil (39325-01-4)	118	65	24	53	46	53	21	46	51	17	46	43	14	40	31
Sipuleucel-T (917381-47-6)	164	52	24	44	45	56	24	50	38	20	33	37	14	20	33
Talimogene laherparepvec (1187560-31-1)	39	20	5	18	12	21	4	18	16	2	20	15	3	20	16
GVAx (917377-71-0)	41	15	1	14	10	11	4	11	11	2	5	7	1	3	5
Contusugene ladenovec (600735-73-7)	8	6	0	4	0	6	0	4	4	0	6	5	0	4	3
Tasadenoturev (1448774-00-2)	9	7	3	5	4	9	2	6	5	0	8	7	0	7	5
Tisagenlecleucel-T (1823078-37-0)	10	2	2	10	9	2	0	10	10	0	2	2	0	3	5
Alipogene tiparvovec (929881-05-0)	1	2	1	0	1	0	2	0	2	0	0	1	0	0	2
INGN 241 (620609-24-7)	7	6	1	3	5	5	4	5	3	1	5	5	0	5	1

Figure 11. Co-occurrence Analysis of Gene and Cell Therapy-Related Substances and Disease Categories

CHAPTER 4. SPECIAL TOPICS: STEM CELL THERAPIES, CAR T-CELL THERAPIES, AND GENE EDITING TECHNOLOGIES

4.1 STEM CELL THERAPIES

As mentioned in the analysis of high-impact documents in Section 2.5, stem cell therapy has been a hot research topic due to its therapeutic potential. Figure 12 shows the growth in the numbers of papers and patents related to stem cells from 1988 to 2017. As can be seen from the figure, most studies on stem cell therapies were published in research papers rather than patents throughout the entire period and the increase in research papers was much more dramatic than patents for each period. The phenomenon may be at least partly due to the legal and ethical debates over the use of stem cells, particularly over germline stem cells, in some countries.

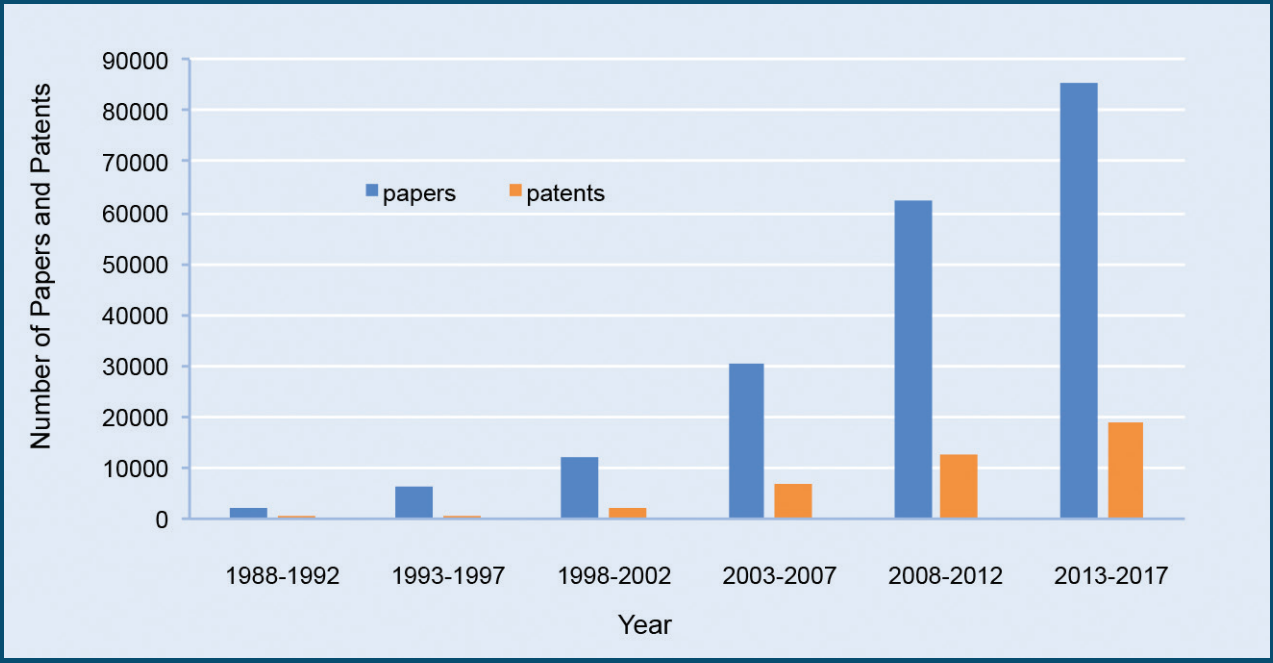


Figure 12. Papers and Patents Related to Stem Cells over Time

There are many types of stem cells, often classified based on their tissues of origin, such as embryonic stem cells (ESC), adult tissue-specific stem cells, induced pluripotent stem cells (iPSC), placental stem cells, etc. Figure 13 depicts the distribution of stem cell research according to the types of stem cells studied and shows that the three most-highly studied stem cell types are mesenchymal stem cells (MSC), hematopoietic stem cells (HSC) and ESC. However, iPSC and neural stem cells have also attracted significant attention.

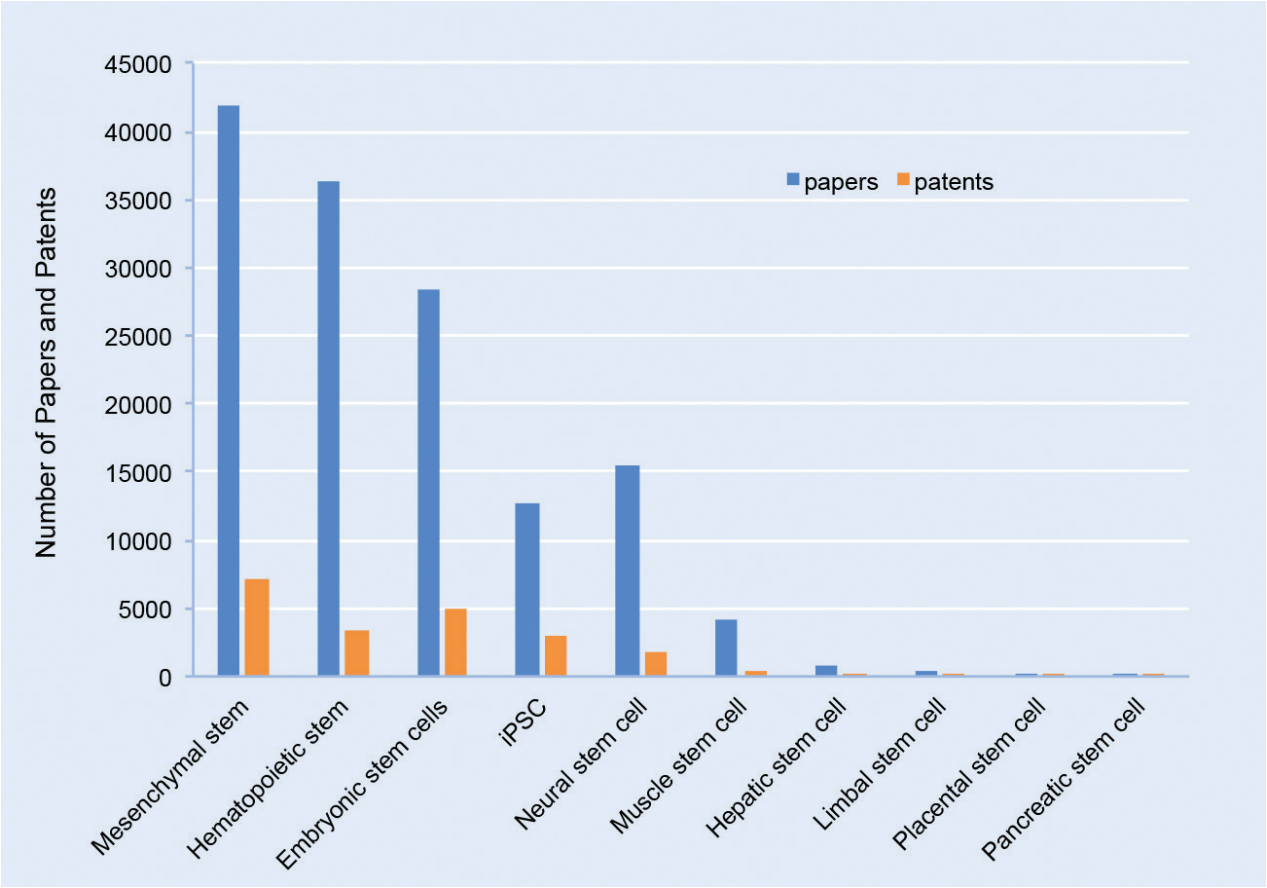


Figure 13. Papers and Patents Related to Specific Types of Stem Cells

Despite significant research on the use of stem cells to restore tissue functions in multiple conditions, only a few stem cell therapies have been approved by government authorities due to various reasons, such as safety concerns. To date, the only stem cell-based treatments approved by the FDA for use in the US are for bone marrow transplants. Canada conditionally approved Prochymal for the treatment of pediatric graft-vs-host disease in 2012[9] and the European Medicines Agency in 2014 approved Holoclar®, a stem cell-based treatment for eye injury[10]. Regardless of the stringent approval guidelines by government authorities, there are still around 5,000 stem cell-related clinical trials ongoing around the world, and about 600 of them are in phase III or IV stages. The disease conditions being investigated include spinal cord injury, blindness, diabetes, myocardial infarction, liver degeneration, neuronal degeneration, chronic lung diseases, renal diseases and blood diseases. Given the significant number of ongoing clinical trials, it is reasonable to predict that the approval rate of stem cell-related treatments may accelerate in the next few years.

4.2 CAR T-CELL IMMUNOTHERAPIES

CAR T-cell immunotherapy, another recent advance in the field of gene and cell therapies, involves genetic modification of a patient's own T-cells to express a chimeric antigen receptor (CAR) specific for a tumor antigen. The genetically modified T-cells then can be expanded *ex vivo* and re-infused back into the patient to allow them to recognize and destroy the tumor antigen-bearing cancer cells. This gene- and cell-based immunotherapy thus boosts the patient's own immune system to fight cancer. As the documents in Table 4 show, CAR T-cell-related patents account for close to 50% of the high-impact patent list. Even more significant is that two recently FDA-approved gene and cell therapy products, Tisagenlecleucel (KYMRIAH®) and Axicarbtagene ciloleucel (YESCARTA®) are both CAR T-cell therapies targeting CD19 for treatment of B-cell malignancy (Table 6). In order to assess the paper and patent publication patterns related to CAR T-cell therapies, a historical trend analysis was performed. Figure 14 shows the dramatic increase of paper and patent numbers related to CAR T-cell therapies in the most recent 5 years.

Table 6. Approved Cell Immunotherapy Products

Product Name	Original Research Organization	Disease Indication	Cell Type	Approving Country and Year
Tisagenlecleucel	Novartis	Precursor B-cell acute lymphoblastic leukemia	CAR T-cell	USA 2017
Axicarbtagene ciloleucel	Kite Pharma	Large B-cell lymphoma	CAR T-cell	USA (2017)
APCEDEN	APAC Biotech	Prostate/ovarian/ colorectal/non-small-cell lung cancer	Dendritic cell	India (2017)
Sipuleucel-T	Dendreon	Prostate cancer	Dendritic cell	USA (2010)
Immuncell-LC	Green Cross Cell Corp	Liver cancer	Dendritic cell	South Korea (2008)
CreaVax-RCC	JW CreaGene Inc	Renal cell carcinoma	Dendritic cell	South Korea (2007)
DCVax-Brain	Northwest Pharmacy	Brain cancer	Dendritic cell	Switzerland (2007)
HybriCell	Genoa Biotecnologia SA	Melanoma, renal cell carcinoma	Fusion of dendritic cells and tumor cells	Brazil (2005)

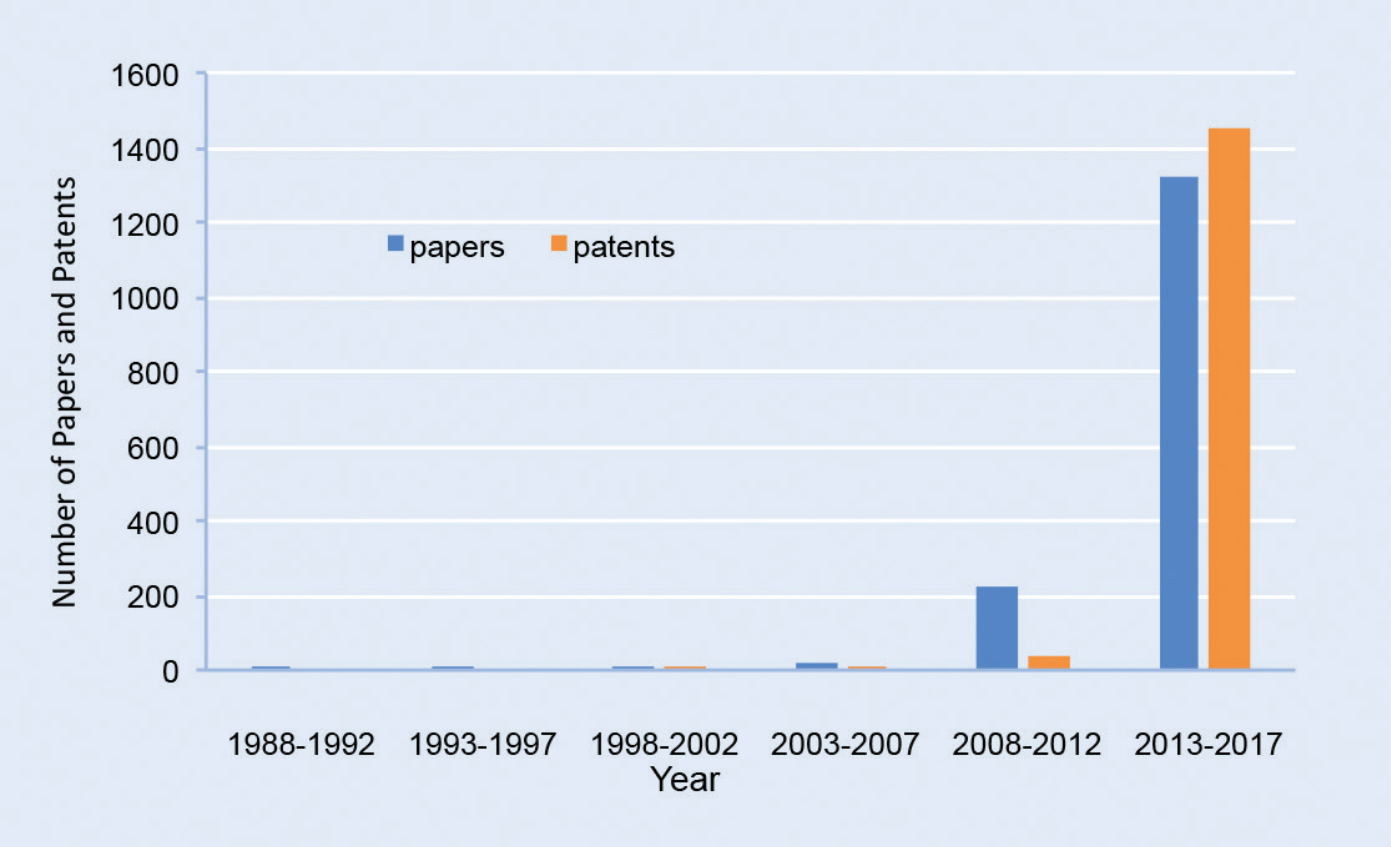
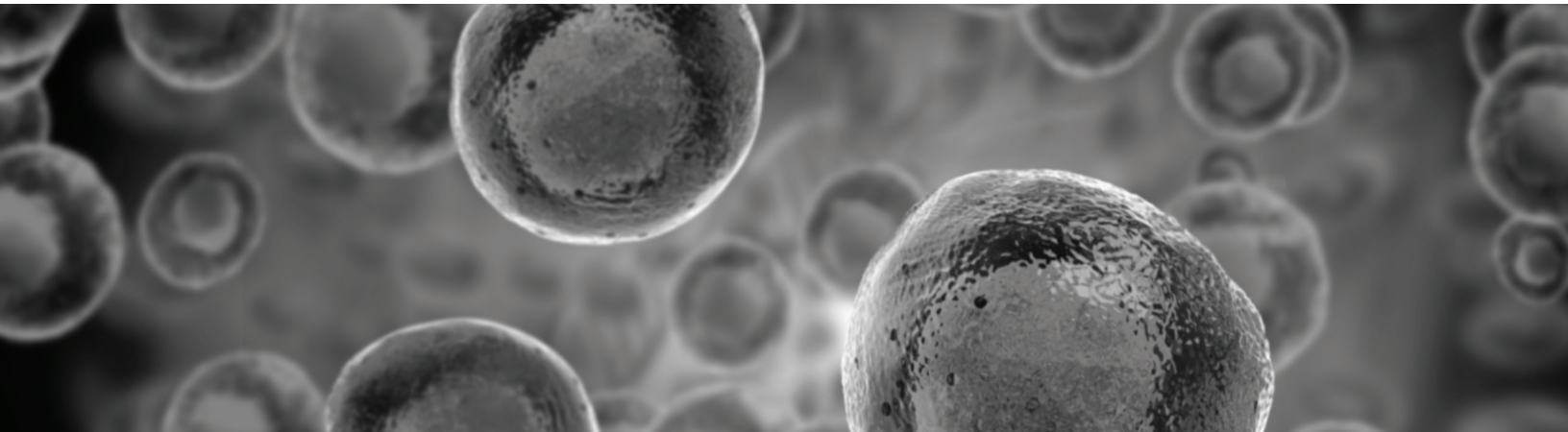


Figure 14. Papers and Patents Related to CAR T-Cell Therapies

Besides CD19, a transmembrane protein expressed at high levels in malignant B-cells, various targetable biomarkers have been studied for CAR T-cell development in the recent 10 years. These targetable biomarkers are associated with the surface of malignant cells and serve as targets for directing cytotoxic T cells to the malignant cells. In order to show how these targetable biomarkers may have been studied in generating CAR T-cell therapies, a list of targetable biomarkers was identified from currently active FDA clinical trial data. A document search was then performed in the CAS database with these targetable biomarkers. Figure 15 shows the number of documents associated with each targetable biomarker for CAR T-cell therapies. Among them, CD19 is the most studied type, followed by CD20, HER2 and CD30. This expansion of targets for CAR T-cell therapies has led to promising results in terms of patient outcome, and has also broadened the potential of CAR T-cell therapies in treating different types of human cancers.



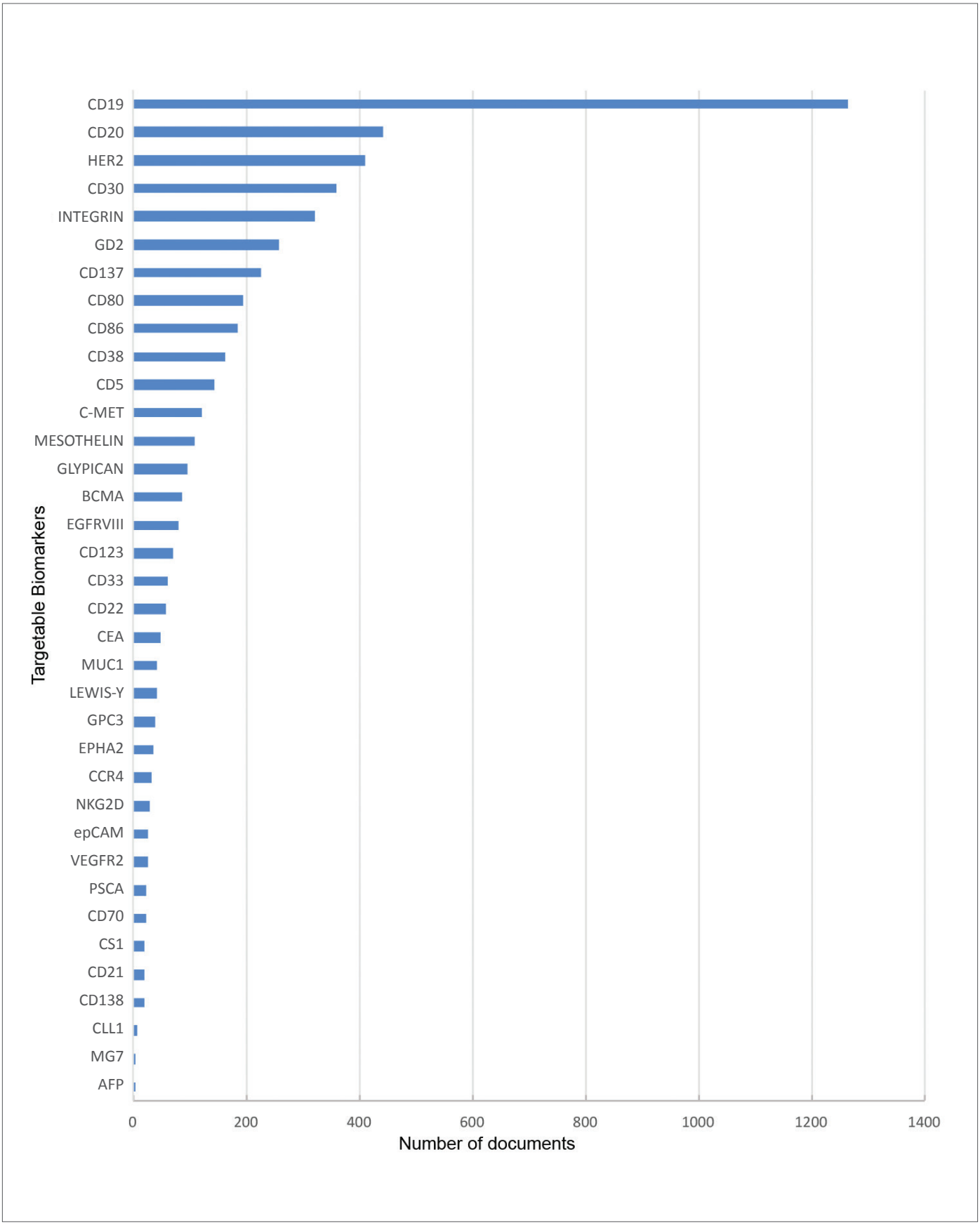


Figure 15. Documents Associated with Possible Targetable Biomarkers for CAR T-Cell Therapies

4.3 GENE EDITING TECHNOLOGIES

Gene editing, also referred to as genomic editing, encompasses a group of technologies that provide scientists with the ability to specifically modify an organism's DNA. Gene editing technologies have traditionally been named according to the types of engineered nucleases used in each technology: meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector-based nucleases (TALENs), and the CRISPR-Cas9 system. These technologies allow genetic material to be added, removed, or altered at particular locations in the genome. By incorporating these new tools in gene therapy, scientists have been able to achieve new medical breakthroughs. Among the available gene editing technologies, the CRISPR-Cas9 system has generated much excitement in the scientific community because it is cheaper, more accurate and more efficient than other existing genome editing technologies. These technologies, especially the CRISPR-Cas9 system, have greatly expanded the scope of gene therapy so that it is becoming a popular strategy for clinical research. Current gene editing technologies have been mostly used to treat HIV, leukemia and hemophilia-related diseases. Analysis of paper and patent publications related to therapeutic gene editing shows that after their initial appearance in 2003, both paper and patent numbers significantly increased during 2008-2017 and the increase in patents was even more dramatic, which is consistent with the strong desires for organizations to own the intellectual properties of such powerful technologies.

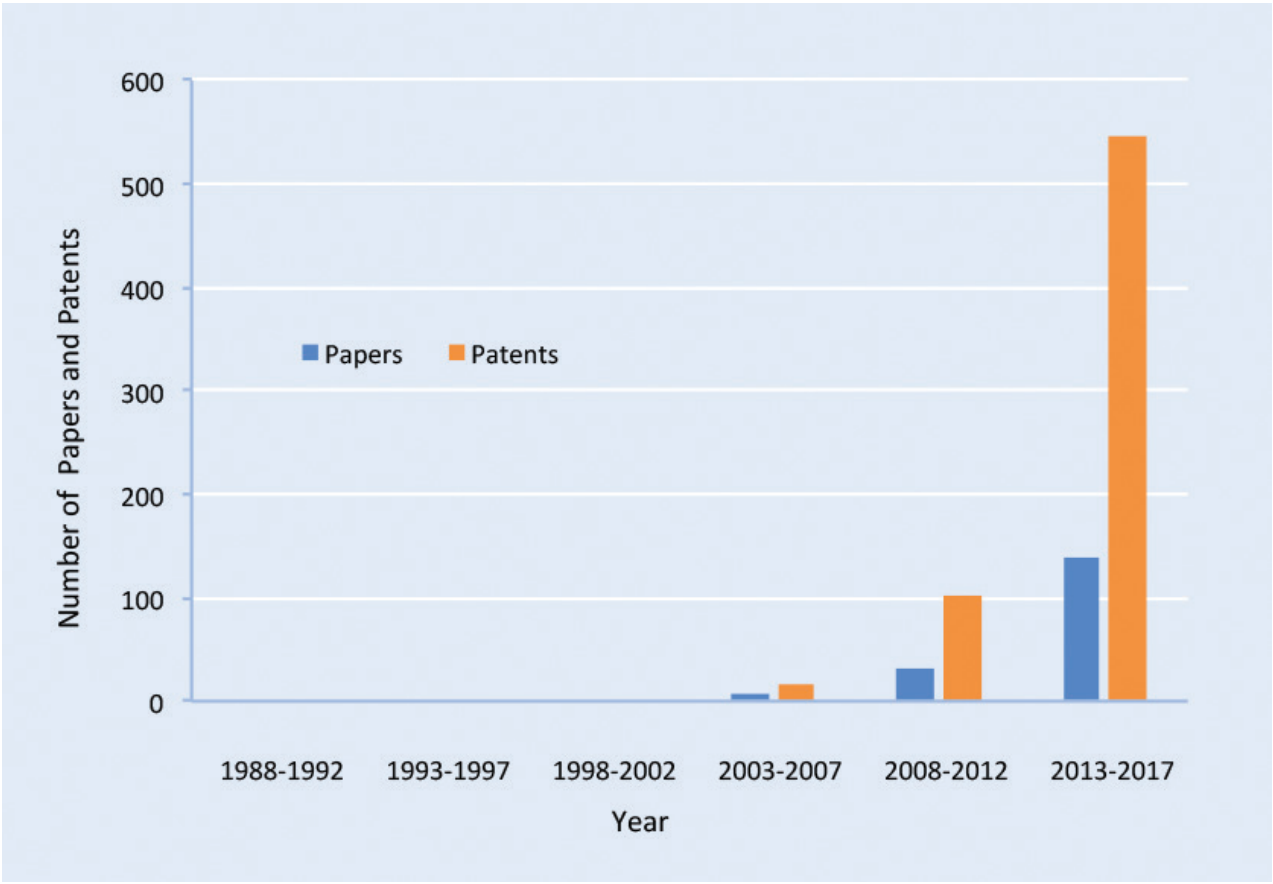


Figure 16. Papers and Patents Related to Gene Editing Technologies

CAS has registered a substantial number of gene editing-related substances. Of these, the ones with clinical applications or drug development potential were extracted and categorized according to the nature of the substances. Figure 17A shows that 85% of the clinically relevant gene editing substances are CRISPR-related substances. Among them, most are different types of CRISPR-associated endonucleases, some are single guide RNA (sgRNA) sequences which function to guide the CRISPR complex to the proper site on the genomic DNA, and some are CRISPR dispersed repeat sequences, as shown in Figure 17B. Other types of gene editing technology-related substances, such as transcription activator-like effector-based nucleases (TALENs), zinc finger nucleases (ZFNs) and meganucleases, account for a relatively small percentage of the substances, as shown in Figure 17A.

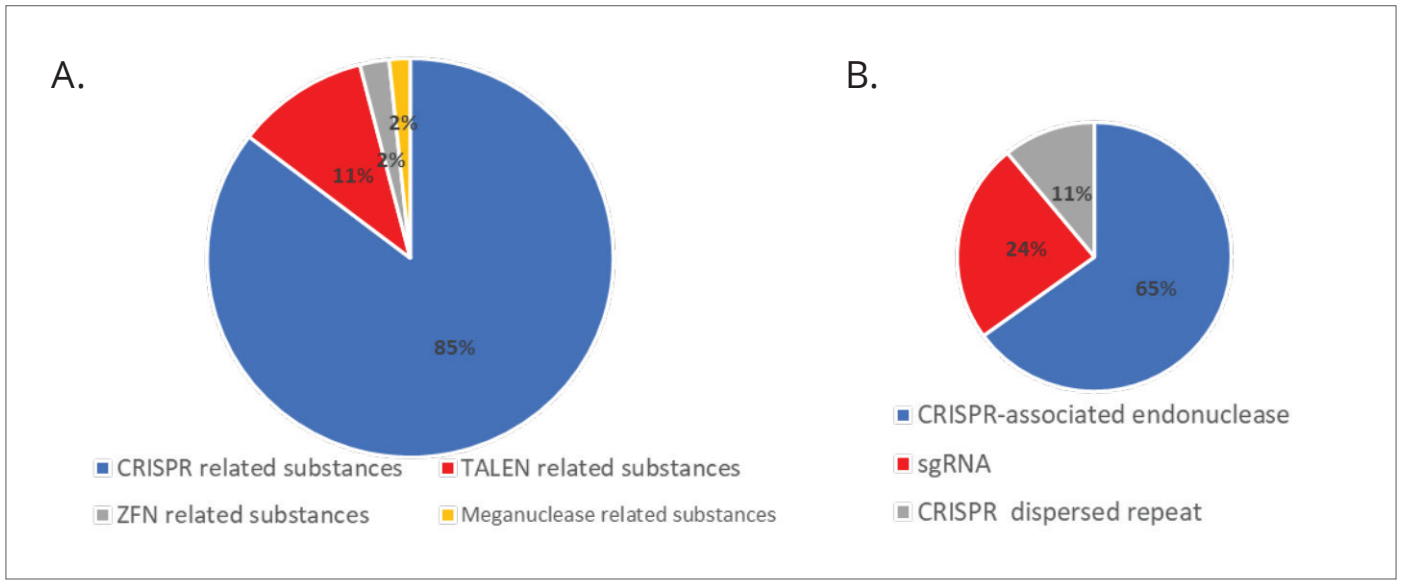


Figure 17. Classification of Substances Related to Gene Editing Technologies.

A: Substances related to gene editing technologies,
B: Further categorization of substances related to CRISPR technology

CHAPTER 5. SUMMARY

In recent decades, the R&D in gene and cell therapy has diversified rapidly beyond initial early studies related to blood and bone marrow transplantation. This is reflected in the continuous increase in numbers of published papers and patent applications. As of 2017, the numbers of papers and patent application families in this field were 120,664 and 37,724, respectively.

These gene and cell therapy papers and patents have focused on the special interest areas related to Pharmacology, Immunohistochemistry, Mammalian Pathological Biochemistry, Biochemical Genetics, and Pharmaceuticals. Over the 30-year period of 1988-2017, the United States, China, Japan, Germany, and the United Kingdom were the top five paper-publishing countries in the field of gene and cell therapies, while the top five countries in terms of patent applications were the United States, China, Japan, South Korea, and Germany. As shown in the patent flow analysis, the United States, Germany, and Japan demonstrated a greater effort in protecting their patented technologies in overseas markets.

The United States is a strong leader in the field of gene and cell therapy R&D as indicated by the fact that most of the major organizations involved are located in the United States. The organizations publishing research papers related to gene and cell therapies are primarily universities and research institutes, while patent applicants are primarily universities, corporations and research institutes.

Primary research topics related to gene and cell therapies associated with the indexed documents include stem cells and stem cell transplantation, anti-cancer research, and the relationships between probiotics and tumors. In addition, due to the advent of gene editing technologies and CAR T-cell therapies, immunotherapy has become an attractive topic. As indicated by the evolution of research topics, many breakthroughs have been made in gene and cell therapies, including the first non-hematopoietic stem cell therapy and multiple approved CAR T-cell therapies. Clinical trials in this field have increased significantly.

In recent years, the growth rate of gene and cell therapy-related substances in the CAS substance collection has accelerated significantly. From 1988 to 2017, a total of 5,233 gene and cell therapy-related substances were added to CAS Registry℠. This includes 2,867 which were registered from 2013-2017, accounting for 55% of the total. The most studied substances include Picibanil (lyophilized Streptococcus cells with anti-tumor activity), Sipuleucel-T (prostate cancer vaccine), Talimogene laherparepvec (immunotherapeutic and oncolytic virus), and GVAx (cancer vaccine).

In this report, the special topics of stem cell therapies, CAR T-cell therapies, and gene editing technologies were also investigated. More types of stem cells have been studied in recent years, such as iPSC, and placenta stem cells. Several stem cell therapies originated from limbal stem cells or mesenchymal stem cells were approved by several governmental authorities. The innovative CAR T-cell therapy has evolved rapidly in the last five years, as reflected by the sharp increase in the numbers of both papers and patents and the quick approval of two therapies. In recent years, the targets of CAR T-cells have also been expanded to more types of cancer and tissues. CRISPR-Cas9, a new gene editing technology, allows genetic changes in human cells to be made easily with much greater efficiency and precision than before. This is especially true for engineered ESCs or iPSCs, which are more difficult to transfect. The combination of CRISPR-Cas9 and CAR T-cells may also lead to further improvement in efficiency and safety of CAR-T cells, improving their anti-tumor efficacy and the production of universal CAR T-cells.

CHAPTER 6. OUTLOOK

Although gene- and cell-related therapies have not yet entered the stage of large-scale commercialized clinical use, there has been a surge of gene and cell therapy products entering the early development stage[11] as a result of significant advances in R&D. This surge, along with technological advances and the early clinical successes of a few FDA-approved gene therapy drugs, indicates great promise in gene and cell therapies.

While bone marrow transplantation has been a lifesaver for the past couple decades, recent news reported that an HIV patient has been free of the virus for 18 months after receiving a hematopoietic stem cell transplantation. These cells contain mutated CCR5 (C-C chemokine receptor type 5) genes which allows the cells to be HIV-resistant. This intriguing finding further confirms the link between hematopoietic stem cells, CCR5 and HIV infection, suggesting that more studies are warranted to elucidate the role of CCR5 in host defense mechanism against HIV and other types of infection[12].

On the other hand, fueled by the clinical success and great potential, CAR T-cell-based therapies will continue to be a major R&D area in gene and cell therapies in the coming years. With ongoing efforts in the development of 1) the second generation of CAR-T cells with enhanced targeting capability and clinical efficacy and 2) universal, "off the shelf" CAR-T cells, it is hoped that the CAR concept and more R&D efforts on CAR-T cell therapies will further optimize clinical outcomes, address undesired side effects such as cytokine storms, lower the cost of this type of treatment, and lead to possibilities to allow such therapies to be applied to more types of cancer.

Safety and precision are two elements essential for gene and cell therapies to be of commercial clinical use. Therefore, it can be expected that more efforts will be directed towards addressing these issues. Accordingly, powerful gene editing technologies, particularly the recently developed CRISPR/Cas systems, have great potential to achieve high levels of precision in gene therapy and will continue to produce new opportunities for gene and cell therapies. The combination of gene editing and CAR T-cell technology may further facilitate the development of gene and cell therapy drugs that are safer and more effective. Continued improvement of expression vectors and gene delivery methods suitable for clinical use will also be a major focus for future design of successful therapies.

Finally, continuing basic research is necessary to further define the relationships between genes and diseases and the complex regulatory networks involved in healthy and diseased cells. Currently, gene therapy has primarily been directed toward a limited number of disease-related genes and targets. Identification of more targets for various diseases will facilitate the development of new gene therapy products. Additional areas for future studies in the area of cell-based immunotherapy include the molecular mechanisms of immune cell migration after their return to the body, preparation of tumor cell-targeting immune cells, mechanisms of tumor cell escape from immune surveillance, and targets for tumor immunotherapy. Stem cells that are derived by dedifferentiation of an individual's own cells could prove to be a valuable new resource for regenerative medicine without risk of incompatibility or immune rejection.

Despite all these challenges, innovative R&D in gene and cell therapies will undoubtedly continue to bring new therapeutic products into the drug development pipeline in the coming years and will have the potential to cure many diseases that are currently difficult to manage. The ongoing significant advent in the R&D of gene and cell therapies will dramatically take the development of biologics to a whole new level.

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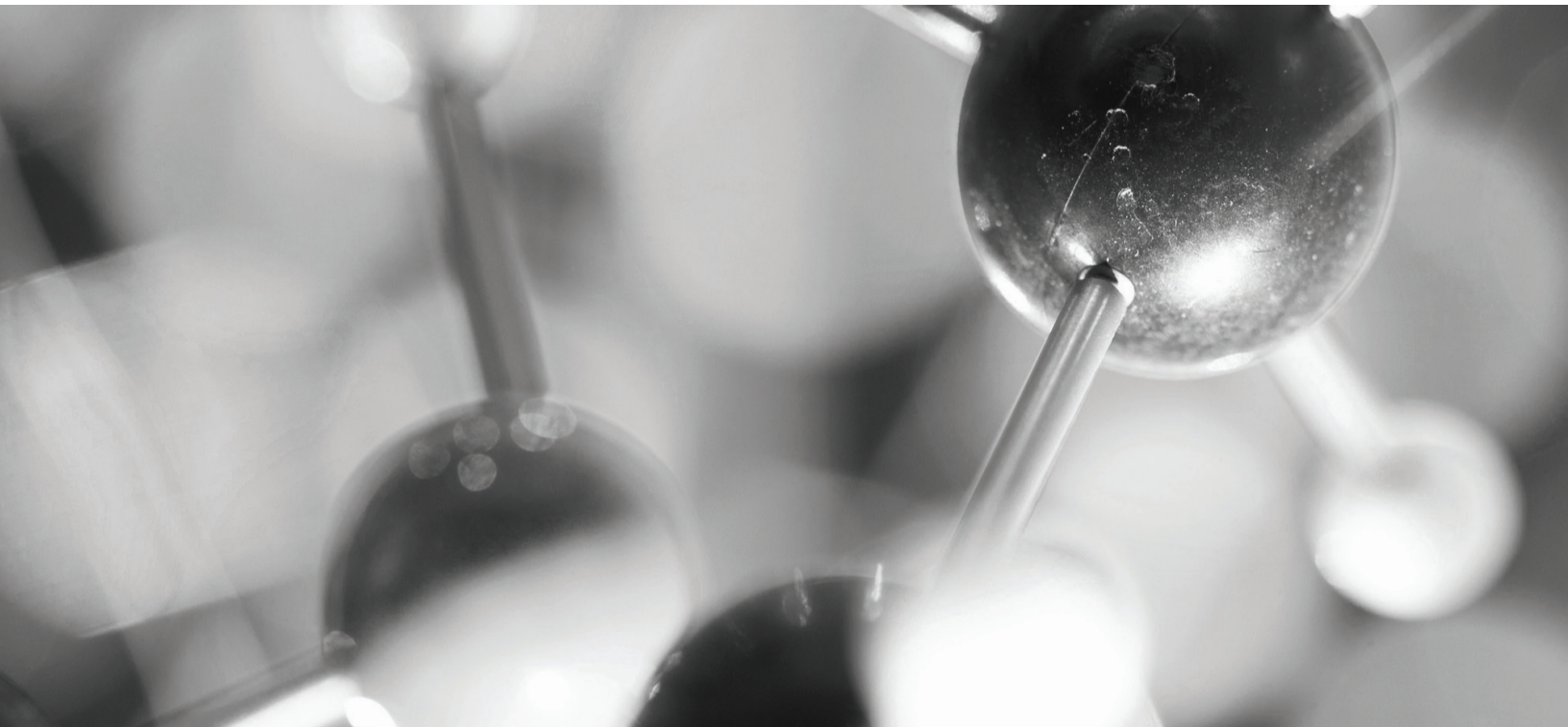

Appendix I. Top 100 Organizations Publishing Papers on Gene and Cell Therapies

Rank	Organization	No. of Papers	Period of Publication	% of Publications in recent 3 years
1	University of California	1940	1970 - 2018	16.91%
2	University of Texas System	1598	1976 - 2018	17.21%
3	National Institutes of Health (USA)	1272	1986 - 2018	13.60%
4	University of Pennsylvania	987	1990 - 2018	17.53%
5	University of Pittsburgh	905	1991 - 2018	9.39%
6	Harvard University	798	1989 - 2018	15.41%
7	Shanghai Jiao Tong University	795	1992 - 2018	18.49%
8	Huazhong University of Science and Technology	757	1997 - 2018	9.11%
9	Osaka University	753	1985 - 2018	6.51%
10	University of Michigan	749	1981 - 2018	13.22%
11	Stanford University	725	1971 - 2018	18.21%
12	Sun Yat-sen University	711	1999 - 2018	13.64%
13	Kyoto University	698	1980 - 2018	10.60%
14	Johns Hopkins University	696	1982 - 2018	14.37%
15	University of Washington	691	1986 - 2018	14.47%
16	Mayo Clinic	686	1985 - 2018	21.75%
17	University of Tokyo	672	1978 - 2018	11.76%
18	Baylor College of Medicine	670	1984 - 2018	8.36%
19	Peking University	656	2000 - 2018	20.43%
20	Sichuan University	630	1999 - 2018	17.14%
21	Fourth Military Medical University of PLA	623	1996 - 2018	11.88%
22	Zhejiang University	599	2000 - 2018	22.37%
23	Third Military Medical University	583	1996 - 2017	11.84%
24	University of Florida	578	1997 - 2018	11.59%
25	Academy of Military Medical Sciences	554	1996 - 2018	14.08%
26	Pfizer Inc.	45	1990 - 2018	11.11%
27	Chinese Academy of Medical Sciences	518	1993 - 2018	14.67%
28	University College London	517	1993 - 2018	18.57%
29	Regents of the University of Minnesota	512	1976 - 2018	19.92%
30	University of Alabama	489	1992 - 2018	8.18%
31	Fudan University	486	1990 - 2018	13.37%
32	Sloan-Kettering Institute for Cancer Research	477	1983 - 2018	27.04%
33	Second Military Medical University	472	1993 - 2018	10.17%

Rank	Organization	No. of Papers	Period of Publication	% of Publications in recent 3 years
34	Kyushu University	463	1984 - 2018	6.70%
35	Chinese Academy of Sciences	462	1985 - 2018	25.54%
36	Fred Hutchinson Cancer Research Center	462	1986 - 2018	14.72%
37	Duke University	455	1993 - 2018	13.19%
38	Southern Medical University	449	1998 - 2018	14.25%
39	University of Toronto	409	1986 - 2018	14.43%
40	Karolinska Institutet	408	1985 - 2018	18.87%
41	Central South University	406	1997 - 2018	11.82%
42	University of North Carolina	401	1989 - 2018	17.21%
43	Chongqing Medical University	396	1999 - 2018	11.62%
44	Massachusetts General Hospital	395	1983 - 2018	10.63%
45	Universiteit Leiden	392	1985 - 2018	15.31%
46	Imperial College London	390	1979 - 2017	7.95%
47	The Ohio State University	387	1995 - 2018	22.74%
48	Washington University in St. Louis	378	1977 - 2018	20.90%
49	Nagoya University	372	1978 - 2018	11.29%
50	Northwestern University	351	1993 - 2018	10.83%
51	Jilin University	346	2001 - 2018	17.05%
52	Keio University	342	1981 - 2018	13.16%
53	Emory University	341	1989 - 2018	23.17%
54	Okayama University	331	1974 - 2016	5.44%
55	Jichi Medical School	313	1981 - 2018	11.18%
56	University of Southern California	308	1989 - 2018	12.66%
57	Vanderbilt University	305	1989 - 2017	24.59%
58	Shandong University	303	2001 - 2018	13.86%
59	University of Illinois	302	1972 - 2018	14.90%
60	Indiana University	296	1989 - 2018	13.18%
61	Soochow University	292	1997 - 2018	21.58%
62	Hokkaido University	291	1985 - 2018	8.59%
63	Harbin Medical University	289	2000 - 2017	14.19%
64	Icahn School of Medicine at Mount Sinai	288	1986 - 2018	14.24%
65	University of Wisconsin	286	1976 - 2018	13.99%
66	Nanjing Medical University	282	1996 - 2017	13.83%
67	University of Chicago	281	1994 - 2018	14.23%
68	University of Iowa	279	1993 - 2018	12.19%
69	National University of Singapore	277	1993 - 2018	14.80%

Rank	Organization	No. of Papers	Period of Publication	% of Publications in recent 3 years
70	Hannover Medical University	273	1997 - 2017	21.98%
71	Columbia University	271	1974 - 2018	18.08%
72	Yonsei University	267	1994 - 2018	26.22%
73	Cornell University	262	1983 - 2018	12.21%
74	Tianjin Medical University	253	1999 - 2018	12.25%
75	University of Oxford	253	1991 - 2018	20.16%
76	University of Colorado	252	1979 - 2018	13.49%
77	Tohoku University	249	1977 - 2018	4.82%
78	Wuhan University	245	1999 - 2018	14.69%
79	Thomas Jefferson University	243	1993 - 2017	10.29%
80	Dana-Farber Cancer Institute	235	1990 - 2018	18.72%
81	The University of Maryland System	234	1993 - 2018	16.24%
82	China Medical University	229	1997 - 2017	10.92%
83	Yale University	229	1985 - 2018	12.66%
84	Universitaet Heidelberg	225	1987 - 2018	20%
85	Universite Catholique de Louvain	225	1970 - 2017	16%
86	Catholic University of Korea	223	1999 - 2018	30.49%
87	McGill University	219	1993 - 2017	9.13%
88	University of Miami	216	1986 - 2017	18.98%
89	Zhengzhou University	215	2002 - 2018	18.60%
90	Capital Medical University	214	1997 - 2017	24.30%
91	University of Hong Kong	208	1997 - 2018	18.75%
92	State University of New York	205	1971 - 2018	17.07%
93	Hebrew University of Jerusalem	194	1982 - 2018	5.67%
94	McMaster University	194	1993 - 2018	9.79%
95	Case Western Reserve University	193	1991 - 2017	14.51%
96	Brigham and Women's Hospital	190	1993 - 2018	14.74%
97	Xi'an Jiaotong University	189	2000 - 2017	17.46%
98	Yeshiva University	188	1991 - 2018	6.91%
99	Jinan University	186	1999 - 2017	17.20%
100	Hanyang University	184	1983 - 2018	23.37%

Appendix II. Top 100 Organizations Publishing Patents on Gene and Cell Therapies

Rank	Organization	No. of Papers	Period of Publication	% of Publications in recent 3 years
1	GlaxoSmithKline	896	1988 - 2018	0.95%
2	University of California	565	1983 - 2018	27.30%
3	U.S. Department of Health and Human Services	332	1989 - 2018	21.15%
4	University of Texas System	304	1991 - 2018	21.05%
5	Novartis AG	294	1964 - 2018	25.42%
6	University of Pennsylvania	291	1994 - 2018	37.11%
7	Chinese Academy of Sciences	280	1998 - 2018	45.85%
8	Institut National de la Sante et de la Recherche Medicale	262	1993 - 2018	43.51%
9	Johns Hopkins University	253	1989 - 2018	21.34%
10	Sanofi	247	1987 - 2017	2.92%
11	Massachusetts General Hospital	229	1988 - 2018	19.65%
12	Seoul National University	224	2002 - 2018	32.42%
13	Societe des Produits Nestle S.A.	224	2000 - 2017	20.09%
14	Incyte Corp.	216	1998 - 2004	0%
15	Harvard University	191	1993 - 2018	34.55%
16	Kyoto University	187	2000 - 2018	35.29%
17	Columbia University	183	1989 - 2018	23.08%
18	F. Hoffmann-La Roche & Co. AG	178	1991 - 2018	15.65%
19	Academy of Military Medical Sciences	175	2001 - 2017	29.71%
20	Massachusetts Institute of Technology	173	1994 - 2018	32.16%
21	Centre National de la Recherche Scientifique	172	1996 - 2018	32.56%
22	Leland Stanford Junior University	160	1989 - 2018	25.62%
23	University of Florida	160	1995 - 2017	24.05%
24	Johnson & Johnson	156	1996 - 2018	11.92%
25	Pfizer Inc.	141	1991 - 2017	3.65%
26	Baylor College of Medicine	135	1992 - 2018	21.05%
27	Guangzhou SALIAI Stemcell Science and Technology Co., Ltd.	131	2015 - 2018	100%
28	University of Pittsburgh	126	1992 - 2018	24.60%
29	Zhejiang University	125	2003 - 2018	30.40%
30	Merck and Co., Inc.	123	1993 - 2017	7.56%
31	Agency for Science, Technology & Research	121	2004 - 2018	36.36%
32	University of Michigan	119	1992 - 2017	10.17%

Rank	Organization	No. of Papers	Period of Publication	% of Publications in recent 3 years
33	Yonsei University	117	2002 - 2018	45.30%
34	Chinese Academy of Medical Sciences	111	1996 - 2018	28.44%
35	Sloan-Kettering Institute for Cancer Research	111	1994 - 2018	57.66%
36	Brigham and Women's Hospital	109	1993 - 2018	29.63%
37	Takeda Pharmaceutical Co., Ltd.	107	1996 - 2017	4.67%
38	University of Southern California	103	1992 - 2018	20.59%
39	Amgen Inc.	102	1988 - 2017	6.06%
40	Children's Medical Center Corp.	100	1994 - 2018	23%
41	Yeda Research and Development Co. Ltd.	99	1993 - 2017	21.21%
42	Sun Yat-sen University	94	2003 - 2018	45.16%
43	University of North Carolina	94	1995 - 2018	27.96%
44	Japan Science and Technology Agency	93	2000 - 2017	2.17%
45	University College London	93	1999 - 2018	46.24%
46	Duke University	91	1995 - 2018	18.68%
47	Dana-Farber Cancer Institute	90	1995 - 2018	45.56%
48	Shanghai Jiao Tong University	89	1999 - 2018	43.82%
49	Wisconsin Alumni Research Foundation (WARF)	88	1996 - 2018	21.59%
50	Merck KGaA	87	1996 - 2017	8.33%
51	Korea Research Institute of Bioscience and Biotechnology	86	2002 - 2017	37.21%
52	Cornell University	85	1996 - 2018	25%
53	Korea University	85	2005 - 2018	44.71%
54	Bristol-Myers Squibb	83	1993 - 2017	6.10%
55	Second Military Medical University	83	2002 - 2017	38.55%
56	Osaka University	79	2006 - 2018	34.18%
57	Peking University	79	2003 - 2017	37.18%
58	Regents of the University of Minnesota	79	1992 - 2017	34.18%
59	The Scripps Research Institute	79	1993 - 2017	16.46%
60	UAB Research Foundation	78	1994 - 2017	7.69%
61	Case Western Reserve University	76	1994 - 2017	17.11%
62	Yale University	76	1996 - 2017	17.11%
63	Cedars-Sinai Medical Center	74	1997 - 2018	33.78%
64	Bayer AG	73	1985 - 2017	5.63%
65	Keio University	70	2001 - 2018	32.86%

Rank	Organization	No. of Papers	Period of Publication	% of Publications in recent 3 years
66	Mondobiotech Laboratories AG	70	2009 - 2012	0%
67	Fudan University	69	2002 - 2018	33.82%
68	Icahn School of Medicine at Mount Sinai	69	1996 - 2017	15.15%
69	Mayo Clinic	68	2000 - 2017	30.88%
70	University of Iowa	68	1995 - 2017	17.65%
71	Emory University	67	1995 - 2017	29.85%
72	Anthrogenesis Corp.	66	2002 - 2017	33.33%
73	University of Washington	66	1994 - 2018	31.82%
74	University System of Georgia	66	1995 - 2017	16.92%
75	Fourth Military Medical University of PLA	65	2002 - 2018	31.25%
76	AstraZeneca	64	1997 - 2018	7.41%
77	Nagoya University	64	2001 - 2018	32.81%
78	Sichuan University	64	2003 - 2018	39.06%
79	University of Massachusetts	63	1993 - 2018	26.98%
80	Third Military Medical University	62	2006 - 2018	29.03%
81	University of Illinois	61	1996 - 2017	13.56%
82	RIKEN (Institute of Physical and Chemical Research)	60	1999 - 2018	21.67%
83	Salk Institute for Biological Studies	60	1992 - 2018	18.33%
84	University of Rochester	60	1990 - 2017	10%
85	University of South Florida	60	1997 - 2018	20%
86	University of Tokyo	60	1997 - 2018	31.67%
87	Consejo Superior de Investigaciones Cientificas (CSIC)	59	2000 - 2017	13.56%
88	Fred Hutchinson Cancer Research Center	59	1993 - 2017	44.07%
89	City of Hope	58	1998 - 2017	36.21%
90	Institut Pasteur	58	1993 - 2017	19.30%
91	Medtronic, Inc.	58	1998 - 2014	0%
92	University of Virginia	58	1997 - 2017	14.04%
93	Catholic University of Korea	57	2003 - 2017	8.77%
94	State University of New York	57	1996 - 2018	24.56%
95	Transgene SA	57	1994 - 2017	12.28%
96	Cellectis	56	2002 - 2018	66.07%
97	New York University	56	1992 - 2018	17.86%
98	National University of Singapore	55	2000 - 2018	36.36%
99	University of Utah	55	1995 - 2018	24.53%
100	Cleveland Clinic Foundation	53	1998 - 2017	22.64%

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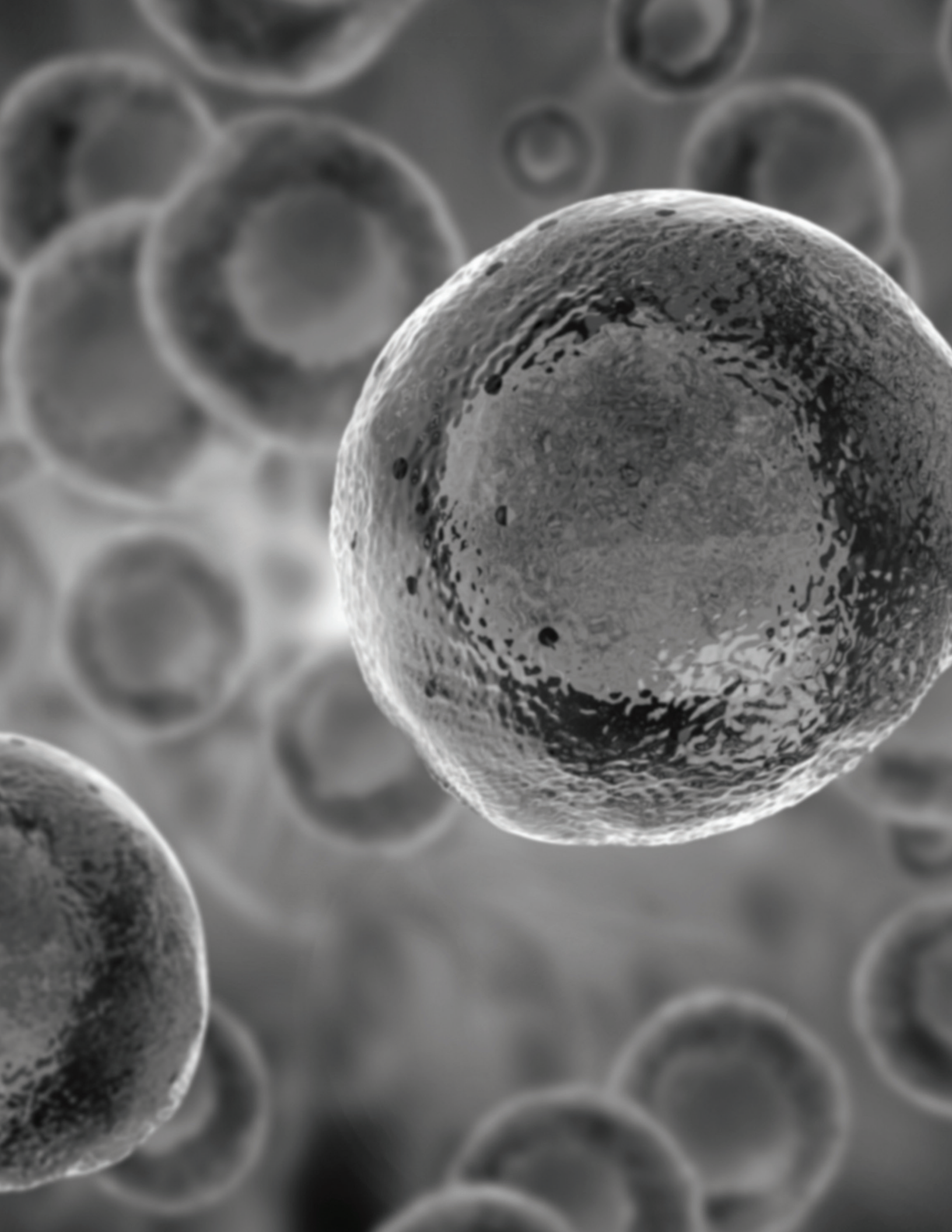

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