VIII. Medicine & Health

1 Engineering research hotspots and engineering research focus

1.1 Development trends of engineering research hotspots

The top 9 engineering research hotspots in medicine and health include basic medicine, clinical medicine, medical informatics and biomedical engineering, pharmacy, imaging and nuclear medicine, public health and preventive medicine, and other subjects (Table 1.1.1). Traditional research has focused on "Stem cells and regenerative medicine," "Molecular imaging technology," "Target therapy for chronic myeloid leukemia," "Sudden cardiac death," "Potential new tactics for preventing type 2 diabetes," "Robot-assisted surgery," "Femtosecond laser-assisted cataract surgery," and "Cerebral arteriovenous malformations." Currently, "Chimeric antigen receptor T-cell immunotherapy" is an emerging hotspots. All core papers regarding these topics published between 2011 and 2016 are listed in Table 1.1.2.

(1) Stem cells and regenerative medicine

Stem cells and regenerative medicine is aimed at boosting wound healing and treatment of diseases through transplantation, differentiation of stem cells, or tissue regeneration, which have enormous potential for clinical applications. Stem cells are rare populations of cells capable of differentiating into multiple types of specialized cells while maintaining their own numbers and identities via self-renewal mechanisms. In mammals, stem cells include: ① Embryonic stem cells (ESCs), which are derived from embryos and can differentiate into any of the three germ layers (i.e., endoderm, mesoderm or ectoderm), and are therefore referred to as pluripotent stem cells (PSCs). Induced pluripotent stem cells (iPSCs) are PSCs that are derived from somatic cells by "reprogramming" (including introduction of specific genes and treatment with chemicals). It is noteworthy that iPSCs allow generation of patient-specific stem cells for therapeutic purpose, thereby bypassing the requirement of embryos. Therefore, iPSCs represent a promising source of cells that may solve for immune rejection in allogenic transplantation. ② Adult stem cells, which are found in various tissues and act as repairing systems of the body by differentiating into specialized cells, e.g., neural stem cells. Presently, stem cells and regenerative medicine have been used widely for treating critical illnesses, including diabetes, stroke, cancer, etc., and have significantly improved health status and quality of life.

(2) Molecular imaging technology

Molecular imaging technology differs from conventional anatomical imaging modalities (including X-ray, ultrasound, CT, and MRI), since a specific molecular imaging agent (tracer or imaging biomarker) is administered via a local injection, intravenously, or via other routes into the living organism or human body, followed by data acquisition using a dedicated

Table 1.1.1 Top 9 engineering research hotspots in medicine and health

No.	Engineering research hotspots	Core papers	Citation frequency	Average citation frequency	Mean year	Proportion of consistently cited papers	Patent-cited publications
1	Stem cells and regenerative medicine	50	2850	57.00	2013.96	30.00%	0
2	Molecular imaging technology	49	4124	84.16	2012.82	30.60%	0
3	Target therapy for chronic myeloid leukemia	49	4472	91.27	2013.12	38.80%	1
4	Chimeric antigen receptor T-cell immunotherapy	49	7880	160.82	2014.06	51.00%	2
5	Sudden cardiac death	48	2381	49.60	2013.00	14.60%	0
6	Potential new tactics for preventing type 2 diabetes	49	3463	70.67	2013.35	24.50%	0
7	Robot-assisted surgery	49	1932	39.43	2013.14	24.50%	0
8	Femtosecond laser-assisted cataract surgery	50	1958	39.16	2013.06	18.00%	1
9	Cerebral arteriovenous malformations	49	1769	36.10	2013.71	26.50%	0

Table 1.1.2 Annual number of core papers belonging to each of the top 9 engineering research hotspots in medicine and health

No.	Engineering research hotspots	2011	2012	2013	2014	2015	2016
1	Stem cells and regenerative medicine	4	8	5	10	15	8
2	Molecular imaging technology	8	14	11	11	5	0
3	Target therapy for chronic myeloid leukemia	7	12	7	14	9	0
4	Chimeric antigen receptor T-cell immunotherapy	5	3	11	5	15	10
5	Sudden cardiac death	12	6	10	12	6	2
6	Potential new tactics for preventing type 2 diabetes	9	6	7	18	4	5
7	Robot-assisted surgery	7	10	15	6	8	3
8	Femtosecond laser-assisted cataract surgery	7	8	16	13	6	0
9	Cerebral arteriovenous malformations	2	9	6	18	12	2

single imaging modality (including PET, SPECT, MRI, ultrasound, optics, photoacoustics, Cherenkov, Raman, or quantum dot imaging, etc.) or a multi-modality fused imaging system, image reconstruction, and processing. Molecular imaging is an integrated research discipline that enables visualization, characterization, and quantification of biochemical processes such as distribution, metabolic changes, target receptor binding, and biological behaviors in vivo at the cellular and subcellular levels through tracking of specific imaging agents. Molecular imaging, which emerged in the late 1990s, is the modern biomedical imaging technology. Industries related to molecular imaging have developed gradually over the past 15 years and have expanded rapidly in recent years. Molecular imaging is a new, interdisciplinary, and highly integrated research and application field, which integrates biological medicine, chemistry, optoelectronics, material science, mathematics, informatics, intelligent manufacturing, and many other disciplines; its application areas initially included mechanistic studies of major human diseases, such as brain science, brain cognition, cancer, cardiovascular diseases, neuropsychiatric disorders etc, later extended to clinical application of individualized diagnosis and treatment as well as precision medicine, which greatly accelerated the development progress of basic and clinical medicine. In addition, it has significantly shortened the research and testing cycles of drug development. For example, the molecule-targeted drug Imatinib Gleevec® was approved by the FDA for application in patients with gastrointestinal stromal tumor (GIST) in 6 years due to the successful application of FDG-PET molecular imaging technique for monitoring the therapeutic responses in the early phase of clinical trials. Innovation and development of molecular imaging technology would enable precise prediction and theranostics for major diseases (including Alzheimer's disease, cancer, etc.). Therefore, it is important to promote molecular imaging-related research that would significantly reduce the cost of medical care and disrupt the foreign technology monopoly in the high-end medical field.

(3) Target therapy for chronic myeloid leukemia

Target therapy for chronic myeloid leukemia (CML) is an integrated process that comprises synthesis and identification of molecules targeting the BCR-ABL fusion protein based on molecular mechanism of CML, clinical follow-up, and prognosis evaluation. The key obstacles for target therapy of CML include the screening of target molecules, sequential use of tyrosine kinase inhibitors or other molecules, disease monitoring, overcoming resistance, and identifying a path to the cure. Since the late 1990s, the availability of imatinib, a first generation tyrosine kinase inhibitor used for target therapy of CML, has significantly changed long-term survival and quality of life for patients with CML. The aim for CML treatment has changed from achieving a complete cytogenetic response in the past to obtaining a deep molecular response, and finally to develop treatment-free remission and cure for the disease. The techniques for CML monitoring have evolved from cell morphology and chromosome detection to immunophenotype analysis by flow cytometry or minimal residual disease monitoring at the molecular level. The technique for minimal residual disease monitoring has evolved from qualitative PCR

to real-time quantitative PCR, and finally to digital PCR, whereas that for detecting the ABL mutation has developed from first to third generation sequencing. Currently, CML has become a chronic controlled disease from a neoplasm, and finally will be a curable disease.

(4) Chimeric antigen receptor T-cell immunotherapy

Immunotherapy has shown a great potential for cancer treatment, and was named among "the world's top ten scientific and technological breakthroughs" by the Journal of Science in 2013. The chimeric antigen receptor T-cell immunotherapy (CAR-T) has developed rapidly in recent years as a new type of cellular immunotherapy. By using gene recombination techniques, T cells derived from the peripheral blood of patients are modified by CAR to specially recognize tumor-associated antigens. The CAR-T cells are then expanded in vitro and infused back into the patients, where they precisely identify and attack the targeted tumor cells. Compared to conventional T cells, CAR-T cells show better targeting, killing activity, and durability, providing a broad prospect for clinical applications. Selection of the target antigen is a critical determinant for the specificity, effectiveness, and safety of CAR. Currently, only few tumor-specific targets are available, among which CD19 is the most effective and well-studied for the treatment of hematological cancers. CAR-T technology has undergone four generations of optimization and innovation, presenting a promising clinical efficacy in the treatment of various tumors, especially hematological malignancies. Currently, CAR-T is one of the most interesting topics in cancer therapy.

(5) Sudden cardiac death

Sudden cardiac death (SCD) is natural death caused by cardiac problems and is characterized by sudden loss of consciousness within one hour after acute symptomatic outbreak. The key scientific problems are that SCD is paroxysmal and unpredictable, with no aura before its occurrence, and therefore, the survival rate is very low. Methods to prevent the occurrence of SCD, detect early symptoms of SCD, and perform effective cardiopulmonary resuscitation (CPR) for reducing mortality are some of the critical issues to be solved in cardiovascular and emergency medicine. SCD is a disease with multiple causes and risk factors, with 2 out of 3 cases occurring outside hospitals. Globally, SCD is the primary cause of cardiovascular death outside the hospital, with average survival rate in USA being 5% and the global average survival rate < 2%. In addition, it has become the most common cause of death in adults less than 65 years of age. More than 450 000 people experience SCD every year in America. In recent years, the incidence of SCD has also increased significantly with rise in the incidence of cardiovascular disease in China. At present, the main problems are lack of prehospital treatment and basic rescue skills, and insufficient emergency transportation system in urban and rural areas. Even though remarkable progress has been made in determining the pathogenesis, risk factors, prevention, treatment, and patient management of SCD, it is still a significant global health issue with life threatening repercussions. Since the risk factors of SCD lack specific indexes, it is necessary to explore and establish an effective multivariate cooperative model to predict, identify, and control the high-risk population. Prevention and treatment of SCD would require equipping and training the community with the use of automated external defibrillators (AED). Extensive efforts are required to control SCD and reduce its health hazards for the society.

(6) Potential new tactics for preventing type 2 diabetes

Potential new tactics for preventing type 2 diabetes (T2D) include developing novel preventive and therapeutic strategies for controlling the epidemic tendency of T2D. In addition, the responsive efficiency of clinical therapies based on existing preventive measures for T2D plus current epidemiological trends of T2D and new findings in this field have to be reinforced. Key scientific questions include: ① how to achieve precise analytical expressions for the commonalities and heterogeneities of the diabetic population, ② how to develop individualized treatment with lifestyle interventions and medications assisted by deep phenotyping and artificial intelligence, and ③ to identify novel therapeutic approaches for treating overweight and obesity, which are major causes of T2D. In the last 30 years, the increase in the prevalence rate of T2D has paralleled the growth of national economies and significantly increased the risk of cardiovascular diseases, severely threatening public health. However, a low awareness rate, poor control rate, and limited treatment options for T2D are the common difficulties. In the past 5 years, large-scale epidemiological cohorts have been set up. Deep phenotyping and deep sequencing, combined with multi-omics analytical techniques, have been developed and made affordable; genetic structures from population

to individual level and interaction patterns between intestinal flora composition and environment have been revealed; controlled clinical trials to prove therapeutic efficacy for multiple novel treatments have been released successively. All these advances suggest that the strategy for prevention and control of T2D needs readjustment and improvement. Predictably, the direction of this strategic revolution in the future will focus on promoting precise prevention and treatment targeted at both the population and individuals to postpone and reverse the progression of T2D. To achieve this goal, it is crucial to adopt case-controlled research model and artificial intelligence-assisted diagnosis and treatment, and proactively combine deep phenotyping, basic research of gene-environment interactions, and efficacy analysis for lifestyle and medication interventions.

(7) Robot-assisted surgery

Robot-assisted surgery refers to surgeons completing various types of surgery with a special robotic surgery system. It involves many crucial scientific issues, which mainly consist of two aspects, namely, medical engineering and clinical application. The former includes power feedback system, semi-rigid surgical instruments, reality enhancement, and systemic miniaturization. The latter includes efficacy advantages, indication development, training and learning curve, as well as cost-effective investigation. Since the 1980s, robot-assisted surgery has gradually developed to be the forefront of minimally invasive surgery. By the end of 2016, more than 3000 robotic-surgical systems were installed worldwide, and 40 896 cases were completed in China, with more domestic robot-assisted surgery system being clinically tested. Currently, the fundamental concept of robot-assisted surgery is long-distance operation, which implies that the surgeon controls the surgical system through the stereoscopic vision and action calibration systems to complete the operation using surgical instruments. Its main advantages include three-dimensional high-definition vision, intuitive motion control, and simulation of multi-degree freedom of a surgical arm. This method allows flexibility and clear vision even in a small cavity. Its safety and short-term feasibility have been confirmed in thoracic surgery, urology, gynecology and abdominal surgery, and other areas; however, its bottlenecks include its large size, poor mobility, lack of tactile feedback, long preparation time, and high expenditure. With the development of real-time image transmission technology such as big data, artificial intelligence, high-speed internet and fiber optic cable signals, we believe that robot-assisted surgery will gradually move towards an era of intelligent and remote surgery.

(8) Femtosecond laser-assisted cataract surgery

Femtosecond laser-assisted cataract surgery is a surgical approach that utilizes a pulsed near-infrared laser of 1030 nm wavelength as an aid for completing cataract phacoemulsification. Its key scientific features include construction of multilayered corneal self-sealing incisions and limbal relaxing incisions, creating precise and complete lens capsule openings, and pre-dissecting the lens nucleus. Surgical intervention is effective in the treatment of cataract. When the lens opacity affects the patient's life and work, surgery can be performed to replace the opaque lens with an artificial intraocular lens. Since the 1980s, extracapsular cataract extraction and cataract phacoemulsification have become developed surgical methods. The 21st century has seen the wide use of phacoemulsification for its small damage and rapid recovery. In recent years, with the emergence of refractive cataract surgery, precisely intellectualized surgical treatment is becoming a trend. Corneal incision creation, continuous circular capsulorhexis, and nuclear fragmentation are important factors that affect the safety and postoperative outcomes of phacoemulsification. Femtosecond laser, as an ultrashort pulse laser with large instantaneous power, precise focusing, and strong penetration, offers a new choice for addressing this problem. The superiority of femtosecond laser-assisted cataract surgery lies in the programing and standardization of procedures with increased safety, accuracy, and predictability. However, with respect to postoperative visual acuity, refraction, and complications, femto phacoemulsification is not more advantageous than manual phacoemulsification. Integration of the femtosecond laser system with the phacoemulsification system can be expected to reduce the cost of equipment and assist in developing techniques that are superior to conventional phacoemulsification.

(9) Cerebral arteriovenous malformations

Cerebral arteriovenous malformations (AVMs) are direct, abnormal connections between arteries and veins, and are considered congenital lesions arising from aberrant vascular development during the intrauterine period. AVMs occur more often in youth and can cause

cerebral hemorrhage and seizures, which incur high lethality and morbidity. The key issues for AVMs include the mechanistic study of its occurrence and progression by targeting therapy to alter its biological behavior and brain function (including neurological and cognitive function) protection during the surgical treatment. Based on the present research status both in domestic and overseas, AVMs develop dynamically, initiated and modulated by a series of congenital and postnatal factors such as genetic variation, abnormal angiogenesis factors, and epigenetic and microenvironmental changes. The reversal or inhibition of these factors could cause degeneration of AVM behavior, thereby reducing bleeding. However, the nature of the specific factors and their spatial and temporal expression, as well as cross-interactions, remains unknown. With the development of radiological and surgical techniques, multimode radiological methods could be used for pre-operative evaluation and construction of personalized brain images by fusing the structural, functional, and hemodynamic images. Simultaneously, hybrid operation combined by vascular intervention and surgery could be used as a minimally invasive technique. A combination of these methods could be used to achieve personalized treatment and protection of brain function. The developmental trends include clarification of the congenital and postnatal factors contributing to AVM pathogenesis and progression based on large numbers of samples, development of targeting therapy for bleeding prevention, and evolution of multimode radiological imaging and hybrid operation techniques for protecting brain function during treatment of AVMs.

1.2 Understanding of engineering research focus

1.2.1 Stem cells and regenerative medicine

The concept descriptions of stem cells and regenerative has been mentioned in section 1.1 (1).

Although considerable progress has been made in stem cell research and regenerative medicine in recent years, many issues remain unsolved and require attention as mentioned below: ① accurate identification of certain types of stem cells is still difficult, largely owing to the heterogeneity of stem cells and ambiguity of stem cell markers; ② the molecular mechanisms of stem cell fate decisions, including both the intrinsic cellular mechanisms and the niche-mediated regulation of stem cells, are not fully understood; ③ robust methods for generating stem cells for clinical applications under well-defined conditions are required; ④ the functional deficiency (e.g., impaired self-renewal or lineage bias) of the cultured and reprogrammed stem cells, and the low efficiency of differentiation into cells of interest, render obtaining enough cells for clinical applications difficult; ⑤ serious concern about potential immune rejection and oncogenic risks for cells derived from PSCs exists; ⑥ methods for boosting endogenous stem cell production or in situ trans-differentiation for tissue regeneration and repair have to be established to bypass transplantation; and ⑦ methods and the underlying mechanism for derivation of complex structures and organs in vitro should be explored for allogenic and autologous organ transplantation in the future.

Advanced technologies have enabled rapid progress in stem cell research. In particular, several new technologies would be instrumental for solving the issues mentioned above: ① tracing of stem cells in vivo by reporter genes or molecular barcodes, in combination with high-resolution imaging techniques, would facilitate better characterization of various stem cells, as well as their interactions with the surrounding environment; ② single cell technologies for isolation and characterization of stem cell populations at the "omics" level (i.e., genomics, epigenomics, transcriptomics, and proteomics) can delineate the heterogeneity of stem cells and clarify the underlying mechanisms; ③ the recently developed genome-editing approaches are powerful tools for manipulating stem cells for both research and clinical applications; ④ robust, clinical-scale cell culture and expansion methods for certain stem cells (e.g., hematopoietic stem cells) are important but remain challenging; and ⑤ novel materials such as biomimetics and three-dimensional culture methods. Stem cells and regenerative medicine have always been the hotspots for international biomedical research. China has also made several exciting contributions towards stem cell research in recent years while developed countries like the USA and Japan remain the leaders in this area.

The top three countries with the maximum number of core papers on "Stem cells and regenerative medicine" are the USA, Switzerland, and Canada (Table 1.2.1). The top three countries or regions with the average citation frequency are Scotland, Italy, and Japan (Table 1.2.1). The

cooperative network of the top 10 countries with the most core publications output (Figure 1.2.1) show that the USA, Australia, Japan, and Scotland are comparatively more cooperative.

The top three institutions according to the number of publications are the Johns Hopkins University, École Polytechnique Fédérale de Lausanne, and the Harvard University (Table 1.2.2). The top three institutions with average citation frequency are The University of Edinburgh, Brigham and Women's Hospital, and then Harvard University (Table 1.2.2). The cooperative network of the top ten institutions with the most core publications output (Figure 1.2.2) show that the Harvard University, Brigham and Women's Hospital, University of Queensland, and The University of Edinburgh share a more connective tie.

The top 10 institutions producing core papers cited by core papers mainly include Johns Hopkins University, Harvard University and Brigham and Women's Hospital in the USA, École Polytechnique Fédérale de Lausanne in Switzerland, the University of Queensland in Australia, and the University of British Columbia in Canada, etc,

Table 1.2.1 Major producing countries or regions of core papers on the engineering research focus "Stem cells and regenerative medicine"

No.	Country/Region	Core papers	Proportion of core papers	Citation frequency	Proportion of citation frequency	Average citation frequency	Consistently cited papers	Patent-cited publications
1	USA	35	70%	1932	77.22%	55.20	7	0
2	Switzerland	8	16%	300	11.99%	37.50	2	0
3	Canada	7	14%	272	10.87%	38.86	0	0
4	Australia	6	12%	514	20.54%	85.67	1	0
5	Japan	5	10%	515	20.58%	103.00	1	0
6	England	4	8%	185	7.39%	46.25	0	0
7	Germany	4	8%	164	6.55%	41.00	0	0
8	Scotland	3	6%	392	15.67%	130.67	1	0
9	Italy	3	6%	382	15.27%	127.33	2	0
10	The Netherlands	3	6%	299	11.95%	99.67	1	0

Table 1.2.2 Major producing institutions of core papers on the engineering research focus "Stem cells and regenerative medicine"

No.	Institution	Core papers	Proportion of core papers	Citation frequency	Proportion of citation frequency	Average citation frequency	Consistently cited papers	Patent-cited publications
1	Johns Hopkins University	7	14%	399	15.95%	57.00	2	0
2	École Polytechnique Fédérale de Lausanne	7	14%	249	9.95%	35.57	2	0
3	Harvard University	6	12%	560	22.38%	93.33	2	0
4	University of Queensland	6	12%	514	20.54%	85.67	1	0
5	University of British Columbia	5	10%	88	3.52%	17.60	0	0
6	Brigham and Women's Hospital	4	8%	413	16.51%	103.25	0	0
7	The Eunice Kennedy Shriver National Institute of Child Health and Human Development	4	8%	51	2.04%	12.75	0	0
8	The University of Edinburgh	3	6%	459	18.35%	153.00	1	0
9	RIKEN	3	6%	424	16.95%	141.33	1	0
10	Western General Hospital	3	6%	392	15.67%	130.67	1	0

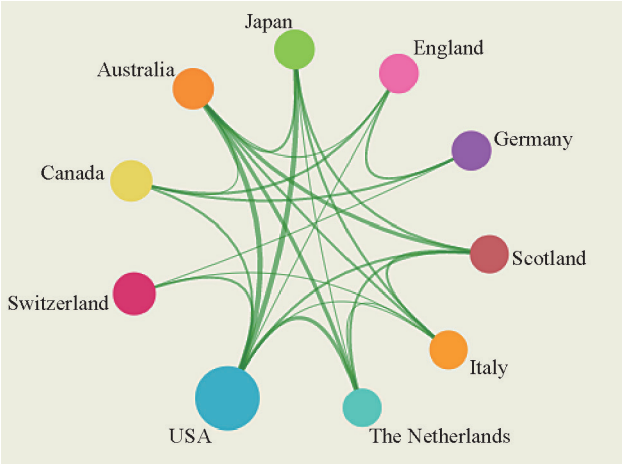

Figure 1.2.1 Collaboration network of the major producing countries or regions of core papers on the engineering research focus "Stem cells and regenerative medicine"[1]

whereas none of the institutions from China is included in the top 10 list (Table 1.2.3 and Table 1.2.4).

1.2.2 Molecular imaging technology

The concept descriptions of Molecular imaging technology has been mentioned in section 1.1 (2).

The current key scientific questions and investigations in the field of molecular imaging (domestic and international) are: ① How to improve the imaging specificity of a specific single molecule or multiple molecules in vivo? ② How to improve the imaging sensitivity of molecules with low concentration? ③ How to improve the imaging resolution for the spatial distribution or dynamic changes of molecules? ④ How to accurately link the computational learning and analysis

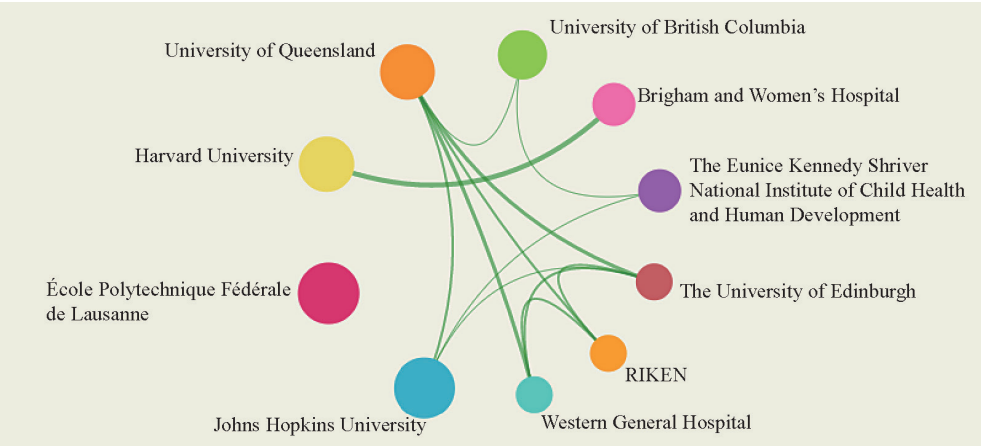

Figure 1.2.2 Collaboration network of the major producing institutions of core papers on the engineering research focus "Stem cells and regenerative medicine"

Table 1.2.3 Major producing countries or regions of core papers that are cited by core papers on the engineering research focus "Stem cells and regenerative medicine"

No.	Country/Region	Number of core papers cited by core papers	Proportion	Mean year
1	USA	28	37.33%	2014.25
2	Canada	6	8.00%	2014.83
3	Switzerland	6	8.00%	2013.83
4	Australia	5	6.67%	2014.20
5	England	4	5.33%	2014.25
6	Germany	4	5.33%	2013.75
7	Japan	4	5.33%	2013.50
8	France	3	4.00%	2013.67
9	The Netherlands	2	2.67%	2015.00
10	Denmark	2	2.67%	2014.50

[1] In the figure, the nodes refer to the countries or regions, the size of the nodes refers to number of papers, the connecting line between nodes refers to papers published based on research cooperation, and the thickness of the connecting line indicates the number of papers based on research cooperation. These are the same in full text.

Table 1.2.4 Major producing institutions of core papers that are cited by core papers on the engineering research focus "Stem cells and regenerative medicine"

No.	Institution	Number of core papers cited by core papers	Proportion	Mean year
1	École Polytechnique Fédérale de Lausanne	6	4.20%	2013.83
2	Johns Hopkins University	6	4.20%	2013.83
3	University of Queensland	5	3.50%	2014.20
4	Harvard University	5	3.50%	2013.60
5	Brigham and Women's Hospital	4	2.80%	2013.25
6	The University of British Columbia	4	2.80%	2015.50
7	Childrens Hosp	3	2.10%	2013.00
8	The Eunice Kennedy Shriver National Institute of Child Health and Human Development	3	2.10%	2015.33
9	Johns Hopkins Med Inst	3	2.10%	2014.67
10	University of Maryland	3	2.10%	2015.00

of medical imaging informatics to the diagnosis and prognosis of diseases?

Internationally, the trends in development of molecular imaging address questions related to translation of new imaging technology and/or molecular probes from preclinical animal model studies to clinical diagnosis and treatment, transformation of the medical applications of molecular imaging from diagnosis to precise therapeutics, early prediction and efficacy evaluation, and other comprehensive, integrated developments.

The research focus on molecular imaging technology includes:

(1) Hardware (including key components and the whole imaging system/instrumentation): Research and development (R & D) on sensing, imaging signal processing; imaging key components and equipment for converting raw data to images.

(2) Software (imaging processing and analysis): Computer processing and deep learning analysis of large image datasets, accurately linking the imaging data to the theranostics and prognosis of diseases; to establish mathematical models and reverse reconstructive algorithms based on investigations on in vivo propagation of light, sound, magnetism, radioactivity, and other physical phenomena, for improving image quality.

(3) Molecular imaging agents (single or multi-modality): Use of small organic molecules, peptides, polymers, nanoparticles, etc. to achieve real-time, rapid image detection at the molecular level. Recently, integrated therapeutic nano-composite has been introduced for imaging corresponding pathological information and targeted therapy via sensing, controlling, and targeting the biological microenvironment of diseases.

(4) Applications: Early diagnosis and detection of malignant tumors, accurate screening of the therapeutic targeted patient population, assessment of various treatment approaches (molecular targeted therapy, radiotherapy, chemotherapy, surgery, etc.) at an early stage; in vivo spatiotemporal dynamic imaging of stem cells or T cell trafficking, evaluation of therapeutic efficacy; early prediction and evaluation of cognitive function and treatment efficacy (aβ and tau protein PET imaging technologies) of Alzheimer's disease; pre-surgery functional localization of epileptic foci (PET and functional MRI); brain function and biochemical map (by PET and functional MRI) generation; neuro-function and neuro-biochemical mapping (PET and functional MRI, etc.).

(5) Studying novel principles and phenomenon-based multimodality imaging methods using multi-modality, multi-functional, multi-target smart molecular probes, and integrated multi-scale, multi-parameter, multi-functional image acquisition and processing; achieve multi-functional fused imaging and early and accurate detection of lesions using real-time multidimensional image trafficking and quantitative analysis of cells or molecules; apply multi-scale fused imaging for lesion localization and complete evaluation; use multi-time point fused imaging for transient imaging and dynamic analysis to achieve

multi-modality molecular imaging for early diagnosis; promote precise prediction, early diagnosis, and treatment of major diseases. China has a large market demand for molecular imaging technology, and its application covers all aspects of the diagnosis, treatment, and prognosis of major diseases. In addition, molecular imaging can be widely used for new drug development and in vivo evaluation. Since molecular imaging is at a critical stage for translating basic science to clinical application both in China and abroad, this is a key opportunity for China to develop molecular imaging technology. The estimated global research and application market for molecular imaging will surpass $100 billion by 2020.

The top 3 countries publishing core papers in the engineering research related to "Molecular imaging technology" are China, Singapore, and Korea (Table 1.2.5), and the top 3 countries or regions with average citation frequency are Taiwan of China, Korea, and Canada (Table 1.2.5). According to the international collaboration network (Figure 1.2.3), the USA, China, Taiwan of China, and Singapore have the maximum number of collaborations.

The top 3 institutions with core patent output are the Fudan University, Chinese Academy of Sciences, and Peking University (Table 1.2.6). The top 3 institutions with average citation frequency are the East China Normal University, Beijing Normal University, and National University of Singapore (Table 1.2.6). According to the collaboration network between major institutions (Figure 1.2.4), collaborations between the Peking University and the Harbin Institute of Technology, and the Jilin University and the Chinese Academy of Sciences are relatively strong.

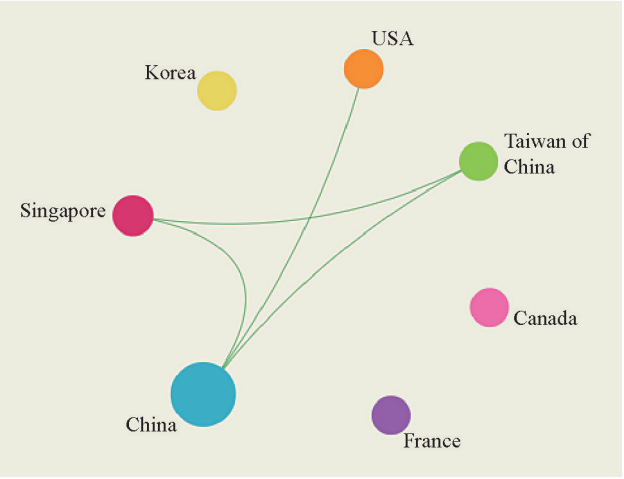

Figure 1.2.3 Collaboration network of the major producing countries or regions of core papers on the engineering research focus "Molecular imaging technology"

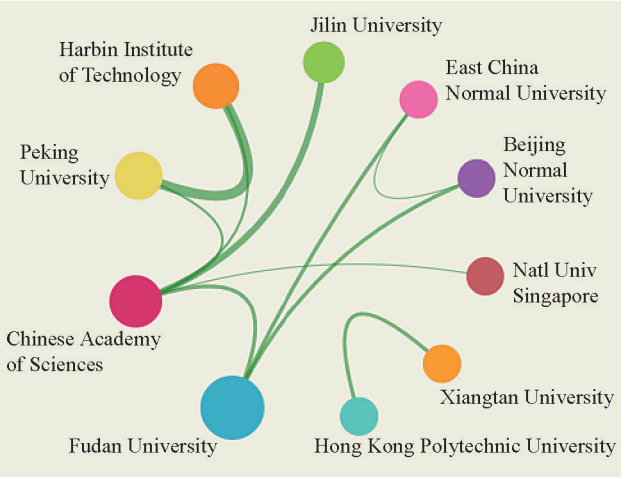

Figure 1.2.4 Collaboration network of the major producing institutes of core papers on the engineering research focus "Molecular imaging technology"

Table 1.2.5 Major producing countries or regions of core papers on the engineering research focus "Molecular imaging technology"

No.	Country/Region	Core papers	Proportion of core papers	Citation frequency	Proportion of citation frequency	Average citation frequency	Consistently cited papers	Patent-cited publications
1	China	41	83.67%	3077	81.14%	75.05	3	0
2	Singapore	4	8.16%	408	10.76%	102.00	0	0
3	Korea	2	4.08%	240	6.33%	120.00	0	0
4	USA	2	4.08%	67	1.77%	33.50	0	0
5	Taiwan of China	1	2.04%	134	3.53%	134.00	0	0
6	Canada	1	2.04%	119	3.14%	119.00	0	0
7	France	1	2.04%	56	1.48%	56.00	0	0

Fort-one core patents on molecular imaging technology have been applied from 2011 to 2016 in China, and institutions such as the Fudan University, Chinese Academy of Sciences, and Peking University have the most core patents, which indicate that China has become the leader in this research area.

The top 10 countries or regions or institutions producing core papers cited by core papers are mainly distributed in the Fudan University, Chinese Academy of Sciences, and Peking University, which shows that China is now a leader in this field (Table 1.2.7 and Table 1.2.8).

1.2.3 Chimeric antigen receptor T-cell immunotherapy

The concept descriptions of chimeric antigen receptor T-cell immunotherapy has been mentioned in section 1.1 (4).

The USA is the first country to start clinical trials of CAR-T. The global registered CAR-T clinical trials were concentrated in the USA before 2010. Europe started to register in 2011, and China in 2013. In 2014, CAR-T was designated a breakthrough therapy by the Food and Drug Administration (FDA) in the USA. There are currently 241 CAR-T clinical trials registered on clinicaltrials.gov worldwide, among which the top three countries are the USA (113), China (99), and Europe (24), respectively. In addition to the conventional therapies, CAR-T will be the most promising therapeutic approach, and is expected to change the landscape of cancer treatment. Although potential risks associated with the clinical use of CAR-T such as off-target effects, cytokine storm and other deficiencies to be improved further, and the anti-tumor effects require further validation for clinical application, it is beyond doubt that this new treatment would bring hope for cancer patients resistant to conventional treatment and is expected to become a novel anti-tumor therapeutic tool. The clinical efficacy of CAR-T therapy will achieve a greater breakthrough by screening of ideal target antigens, exploring the best CAR signal combinations, optimizing host conditions, combining other treatment options, as well as establishing standard operating procedures and

Table 1.2.6 Major producing institutions of core papers on the engineering research focus "Molecular imaging technology"

No.	Institution	Core papers	Proportion of core papers	Citation frequency	Proportion of citation frequency	Average citation frequency	Consistently cited papers	Patent-cited publications
1	Fudan University	19	38.78%	2068	54.54%	108.84	3	0
2	Chinese Academy of Sciences	12	24.49%	751	19.80%	62.58	0	0
3	Peking University	9	18.37%	345	9.10%	38.33	0	0
4	Harbin Institute Of Technology	8	16.33%	212	5.59%	26.50	0	0
5	Jilin University	5	10.20%	220	5.80%	44.00	0	0
6	East China Normal University	3	6.12%	472	12.45%	157.33	0	0
7	Beijing Normal University	3	6.12%	400	10.55%	133.33	1	0
8	Natl Univ Singapore	3	6.12%	396	10.44%	132.00	0	0
9	Xiangtan University	3	6.12%	214	5.64%	71.33	0	0
10	Hong Kong Polytechnic University	3	6.12%	214	5.64%	71.33	0	0

Table 1.2.7 Major producing countries or regions of core papers that are cited by core papers on the engineering research focus "Molecular imaging technology"

No.	Country/Region	Number of core papers cited by core papers	Proportion	Mean year
1	China	35	83.33%	2012.66
2	Singapore	4	9.52%	2013.25
3	France	1	2.38%	2012.00
4	Taiwan of China	1	2.38%	2012.00
5	Korea	1	2.38%	2012.00

quality control system. Recently, companies such as Novartis and Kite submitted applications to the FDA of the USA for approving the commercialization of CAR-T therapies. With accumulation of clinical experience and expansion of scientific research, we expect this novel cellular immunotherapy to be more effective, safe, and widely used for cancer treatment, and to contribute to the development of medicine and human health.

The top 3 countries or regions ranked by core publications related to "chimeric antigen receptor T-cell immunotherapy" research are the USA, Germany, and the UK, respectively (Table 1.2.9), and the top 3 countries ranked by average citation frequency of a paper are Canada, the USA, and Greece, respectively (Table 1.2.9). Germany, the USA, the UK, and Canada collaborate more according to the collaborative network (Figure 1.2.5) of the countries with core paper output. The top 3 institutions ranked by core publications are the University of Pennsylvania, National Cancer Institute, Children's Hospital of Philadelphia, and Memorial Sloan Cancer Center, respectively (Table 1.2.10), and the top 3 institutions ranked by average citation frequency of a paper are the Children's Hospital of Philadelphia, University of Pennsylvania and National Institutes of Health, respectively. According to the cooperation network of the top 10 institutions ranked by core publication output (Figure 1.2.6), there has been greater cooperation between the National Cancer Institute and the National Institutes of Health, between the Children's Hospital of Philadelphia and the University of Pennsylvania.

Table 1.2.8 Major producing institutions of core papers that are cited by core papers on the engineering research focus "Molecular imaging technology"

No.	Institution	Number of core papers cited by core papers	Proportion	Mean year
1	Fudan University	18	21.95%	2012.06
2	Chinese Academy of Sciences	11	13.41%	2012.91
3	Peking University	6	7.32%	2013.67
4	Harbin Institute Of Technology	5	6.10%	2014.20
5	Jilin University	5	6.10%	2013.00
6	Xiangtan University	3	3.66%	2013.33
7	Hong Kong Polytechnic University	3	3.66%	2013.33
8	National University of Singapore	3	3.66%	2012.67
9	Beijing Normal University	2	2.44%	2011.00
10	East China Normal University	2	2.44%	2011.50

Table 1.2.9 Major producing countries or regions of core papers on the engineering research focus "Chimeric antigen receptor T-cell immunotherapy"

No.	Country/Region	Core papers	Proportion of core papers	Citation frequency	Proportion of citation frequency	Average citation frequency	Consistently cited papers	Patent-cited publications
1	USA	44	89.80%	6578	98.50%	149.50	3	2
2	Germany	6	12.24%	148	2.22%	24.67	0	0
3	England	3	6.12%	134	2.01%	44.67	0	0
4	Canada	2	4.08%	611	9.15%	305.50	0	0
5	China	2	4.08%	17	0.25%	8.50	1	0
6	Greece	1	2.04%	49	0.73%	49.00	0	0
7	Qatar	1	2.04%	12	0.18%	12.00	0	0
8	Italy	1	2.04%	8	0.12%	8.00	0	0

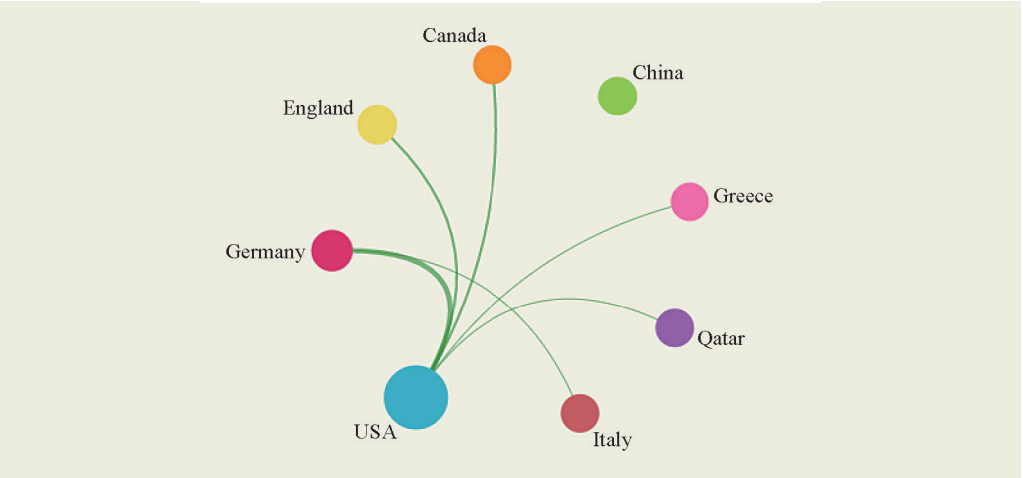

Figure 1.2.5 Collaboration network of the major producing countries or regions of core papers on the engineering research focus "Chimeric antigen receptor T-cell immunotherapy"

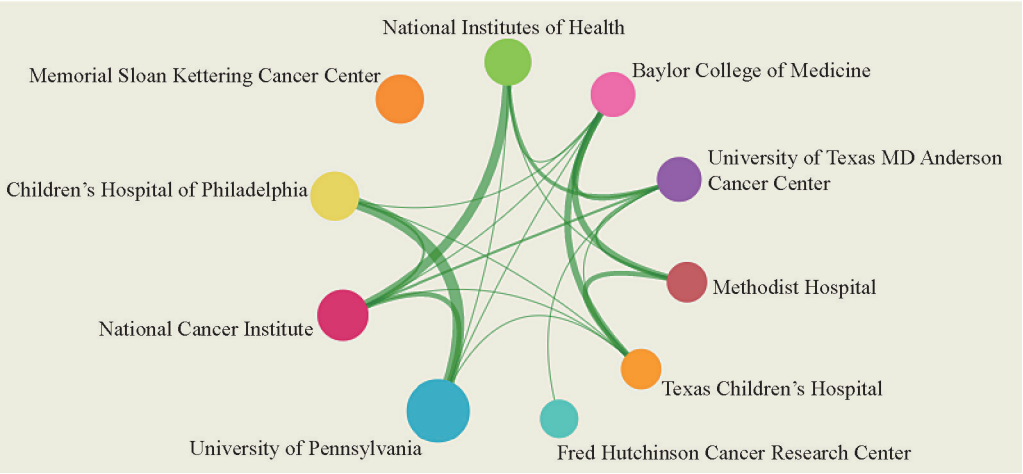

Figure 1.2.6 Collaboration network of the major producing institutions of core papers on the engineering research focus "Chimeric antigen receptor T-cell immunotherapy"

The top 10 countries or regions and research institutions ranked by core papers cited by core papers are mainly concentrated in the university of Pennsylvania, the National Cancer Institute, the Children's Hospital of Philadelphia and the National Institutes of Health (Table 1.2.11 and Table 1.2.12). In general, the USA takes the lead in this field.

2 Engineering development hotspots and engineering development focus

2.1 Development trends of engineering development hotspots

The top 10 hotspots related to engineering development in medicine and health include basic medicine, clinical medicine, pharmacy, medical informatics and biomedical engineering, public health and preventive medicine, and other subjects (Table 2.1.1). "Genome editing" is an emerging hotspot. Conventional research has focused on "Immune cell therapy technology," "Stem cell technologies," "Biomedical materials," "Wearable medical sensors," "DNA sequencing technologies," "Telemedicine," "Precision drugs," "Vaccine preparation," and "Medical imaging techniques." All core patents related to these hotspots published between 2011 and 2016 are listed in Table 2.1.2.

(1) Genome editing

Genome editing originated from genetic engineering

Table 1.2.10 Major producing institutions of core papers on the engineering research focus "Chimeric antigen receptor T-cell immunotherapy"

No.	Institution	Core papers	Proportion of core papers	Citation frequency	Proportion of citation frequency	Average citation frequency	Consistently cited papers	Patent-cited publications
1	University of Pennsylvania	16	32.65%	3272	49.00%	204.50	2	1
2	National Cancer Institute	10	20.41%	1224	18.33%	122.40	2	1
3	Children's Hospital of Philadelphia	9	18.37%	2133	31.94%	237.00	1	0
4	Memorial Sloan Kettering Cancer Center	9	18.37%	1177	17.63%	130.78	0	0
5	National Institutes of Health	8	16.33%	1193	17.86%	149.13	1	0
6	Baylor College of Medicine	7	14.29%	882	13.21%	126.00	0	0
7	University of Texas MD Anderson Cancer Center	7	14.29%	789	11.81%	112.71	0	1
8	Methodist Hospital	5	10.20%	721	10.80%	144.20	0	0
9	Texas Children's Hospital	5	10.20%	720	10.78%	144.00	0	0
10	Fred Hutchinson Cancer Research Center	4	8.16%	173	2.59%	43.25	0	1

Table 1.2.11 Major producing countries or regions of core papers that are cited by core papers on the engineering research focus "Chimeric antigen receptor T-cell immunotherapy"

No.	Country/Region	Number of core papers cited by core papers	Proportion	Mean year
1	USA	34	70.83%	2014.26
2	Germany	5	10.42%	2015.00
3	Canada	2	4.17%	2013.50
4	England	2	4.17%	2013.50
5	China	2	4.17%	2015.50
6	Greece	1	2.08%	2013.00
7	Qatar	1	2.08%	2016.00
8	Italy	1	2.08%	2015.00

in the late 1970s, and since 2000, the discovery of engineered nucleases has advanced the technology. In the past five years, genome editing has become a research hotspot in various fields ranging from basic research to practical applications. Genome editing technology employs programmable nucleases for inducing precise cleavages at specific genome loci. The induced double-strand DNA breaks are fixed via endogenous DNA repair mechanisms, including non-homologous end joining (NHEJ), or, homology-directed recombination (HDR) once a template provided. Currently, three major classes of nucleases have been widely utilized to enable site-specific genome editing including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9. Particularly, CRISPR/Cas9 is more precise and efficient, although it is based on relatively simple design principles. Therefore, it has broadened the potential of genome editing and has proven to be extraordinarily valuable for high-throughput genome

Table 1.2.12 Major producing institutions of core papers that are cited by core papers on the engineering research focus "Chimeric antigen receptor T-cell immunotherapy"

No.	Institution	Number of core papers cited by core papers	Proportion	Mean year
1	University of Pennsylvania	14	11.48%	2014.21
2	National Cancer Institute	9	7.38%	2014.67
3	Children's Hospital of Philadelphia	7	5.74%	2014.00
4	National Institutes of Health	7	5.74%	2014.29
5	University of Texas MD Anderson Cancer Center	6	4.92%	2014.17
6	Memorial Sloan Kettering Cancer Center	6	4.92%	2014.33
7	Fred Hutchinson Cancer Research Center	4	3.28%	2015.00
8	University of Washington	4	3.28%	2015.00
9	Baylor College of Medicine	4	3.28%	2013.25
10	Hackensack University	3	2.46%	2014.67

Table 2.1.1 Top 10 engineering development hotspots in medicine and health

No.	Engineering development hotspots	Published patents	Citation frequency	Average citation frequency	Mean year
1	Genome editing	231	5 430	23.51	2014.13
2	Immune cell therapy technology	654	16 090	24.60	2012.49
3	Stem cell technologies	1 173	21 013	17.91	2012.31
4	Biomedical materials	191	3 125	16.36	2012.19
5	Wearable medical sensors	527	36 151	68.60	2012.66
6	DNA sequencing technologies	480	9 633	20.07	2013.07
7	Telemedicine	31	380	12.26	2012.77
8	Precision drugs	270	7 368	27.29	2012.45
9	Vaccine preparation	765	17 392	22.73	2012.32
10	Medical imaging techniques	179	3 990	22.29	2012.13

Table 2.1.2 Annual number of core patents belonging to each of the top 10 engineering development hotspots in medicine and health

No.	Engineering development hotspots	2011	2012	2013	2014	2015	2016
1	Genome editing	19	3	10	108	79	12
2	Immune cell therapy technology	201	147	149	103	47	7
3	Stem cell technologies	425	281	239	156	56	16
4	Biomedical materials	68	54	38	27	4	0
5	Wearable medical sensors	148	116	95	108	56	4
6	DNA sequencing technologies	102	80	76	137	74	11
7	Telemedicine	9	4	6	9	3	0
8	Precision drugs	80	71	53	51	14	1
9	Vaccine preparation	241	214	176	98	33	3
10	Medical imaging techniques	76	41	37	15	7	3

engineering, attracting great enthusiasm and investments from biomedical research institutes and pharmaceutical companies. The market is expected to surpass $5 billion by 2021.

(2) Immune cell therapy

Immune cell therapy is an immunotherapy-based strategy used for cancer treatment, in which the immune cells collected from the patient's blood are modified and expanded in vitro, and later infused back into the patient. It not only directly kills tumor cells, but also activates the immune system against tumors. Immune cell therapy has a history of more than three decades. With the rapid development in biological technology, the regimens of immune cell therapy have shown notable curative effect on advanced tumors that are resistant to conventional therapies, thus drawing increased attention in the areas of science and medicine. In 2011, Nature reported that immune cell therapy would cause a new round of research upsurge, and might play an important role in cancer therapy in the future. Cancer immunotherapy was first in the list of "the world's top ten scientific and technological breakthroughs" according to Science in 2013, and became the focus of the Science Frontier. In 2016, the USA government launched the "Cancer MoonShot" project, in which immune cell therapy is highly expected to become one of the main approaches for dramatically increasing the therapeutic efficacy of cancer treatment and a practice of precision medicine. This technology is considered one of the most revolutionary technologies, which opens up new ideas for a variety of intractable diseases (tumors, cardiovascular diseases, nervous system diseases, etc.) and brings new hope for conventional incurable diseases, indicating a great potential for application. Immunotherapy has become the fourth cornerstone of cancer treatment along with the other three standard treatments, namely, surgery, chemotherapy, and radiotherapy.

(3) Stem cell technology

Stem cell technology involves harnessing the multipotency of stem cells for remedying, healing or replacing damaged tissues or organs in organisms. Stem cells can be classified into pluripotent stem cells (PSCs) and adult stem cells. PSCs can be then further classified into embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). ESCs are derived from embryos, and can differentiate to any cell type within the three germ layers (i.e. ectoderm, mesoderm, endoderm). iPSCs are pluripotent stem cells genetically reprogrammed from mature somatic cells to embryonic stem cell-like state. With the advent of iPSCs and reprogramming technologies, researchers can circumvent ethical issues of using embryos, while also generating patient-specific PSCs, which may avoid immune rejection in allogenic transplantations. Adult stem cells are undifferentiated cells found in multiple tissues throughout the body, which act as a repair system and replenishes dying cells or damaged tissues by differentiating to various cell types within a specialized tissue, e.g. neural stem cells. Owing to the repairing nature of stem cells, they are widely used in the treatment of several diseases including neurological, hematological, cardiovascular, hepatic, and renal diseases. It is of noteworthy that hematopoietic stem cells transplantation, a paradigm for stem cell therapies, has been broadly used for treating hematological malignancies, which have greatly improved the survival and health status of the patients. With the recent development of reprogramming technologies, pluripotent stem cell-based clinical trials for age-related macular degeneration have already been initiated in Japan. Preliminary reports of the iPSCs-derived retinal transplant in patients showed promising results; however, further clinical investigations are required.

(4) Biomedical materials

Biomedical materials are used for the diagnosis, treatment, repair, or replacement of damaged tissues and organs, or for enhancement of organ functions. In accordance with international practice, its management belongs to the scope of medical devices, accounting for about 40% of the market share of medical devices. According to the composition and properties, these materials are divided into medical metal materials, medical polymer materials, bioceramic materials, and biomedical composite materials. Biomedical materials originated in the mid-40s of last century, and the industry was formed in the 80s of last century. The application of biomedical materials not only saved a large number of lives of critically ill patients, but significantly reduced mortality associated with cardiovascular diseases, cancer, trauma and other major diseases and improved people's health level and quality of life. Thus, it has played a leading role in reforming contemporary medical technology and health care system, and has significantly reduced the cost of medical care.

(5) Wearable medical sensors

Medical sensors and transducers are important devices that transform the parameters and vital signals of the human body into measurable targets. Medical sensors are widely used in medical devices and medical research, from bedside monitors for human physiological parameters (heart rate, blood oxygen, breathing, body temperature, blood pressure, and so on) to the operation room monitors, which require continuous blood pressure monitoring, body temperature monitoring and intensive care unit monitors for measuring blood oxygenation level and intracranial pressure. Medical sensors are also the core components of large medical equipment such as ultrasound, endoscopic surgery robotics, rehabilitation robotics, etc., some of which are used for feedback control. They also find applications in optogenetics, miniature confocal microscopy, traditional Chinese medicine (the so-called "watch-listen-inquiry-touch" diagnostics), as well as in vitro diagnostics. The latest miniature molecular imaging microscope can distinguish tumor cells and normal cells in real time during operation. With the development of semiconductor and material technology, medical sensors are advancing towards miniaturization, implantation, and becoming wireless. Non-invasive wearable medical sensors are increasingly used in daily life for continuous monitoring of blood glucose, ECG, blood pressure, etc. Some of the sensors are be embedded in a variety of clothing, such as sports shoes, underwear, helmets and so on. Wearable medical sensors with various measurement parameters are becoming ubiquitous and transparent to the users. Today's novel electrochemical sensors can detect the human health status by measuring human breath and can determine the resection of benign and malignant cells by detecting smoke from minimally invasive surgery. Researchers are also working on developing point-of-care in vitro diagnostic (IVD) chip, where the electrochemical sensor with high sensitivity can detect small changes of dielectric constants scanned at low or high frequency in different cells, bacteria, and viruses. Implantable medical "wet interface" sensors have entered the mainstream, such as implanted electrode sensors for the brain wet interface, image sensor for the optic nerve and auditory nerve interface, sound sensor for vision and hearing repair, and implanted neural interface for paralyzed patients. Simultaneously, the study of biomimetic extrinsic implant sensors based on synaptic discharge and membrane ion channels is also developing rapidly. With the popularity of sensors, active wearable medical sensors that can take measurements and provide real-time feedback to the receiver have entered the market. For example, brainwave sensors are used to provide meditation feedback and facilitate people to meditate or provide brain wave measurements and stimulation to improve athletes' performance and rehabilitation. Ubiquitous medical sensors have spawned a huge industry of big health data, which has immeasurable social significance for the maintenance of human health.

(6) DNA sequencing technologies

DNA sequencing is the process of determining the precise order of nucleotides (adenine, guanine, cytosine, and thymine) in a particular region of DNA. DNA sequencing technologies have evolved through at least three or four generations from the first-generation Sanger sequencing in 1977. Sequencing technologies now permit genome, epigenome, transcriptome, or protein profiling of single cells sampled from various cell types, as well single cell multi-omics measurements. Decoding of the genome sequence provided a powerful tool for unlocking the mysteries of life, understanding medical genetics, uncovering disease mechanisms, identifying new mutations, diagnosing diseases in prenatal testing, and developing drugs for target therapy of cancer. The advent of single cell sequencing (SCS) enabled understanding of biological heterogeneity, study of the molecular mechanisms of embryo development and gametogenesis, determination of the cause of unexplained infertility, and accurate diagnosis of genetic diseases in pre-implantation embryos. Use of blood samples to examine DNA from tumor cells (liquid biopsy) can detect diseases at an early stage and circumvent the pain of surgery, monitor disease development, and custom-design treatment. Additionally, as a safe and reliable method for identifying affected fetuses before birth, non-invasive prenatal diagnosis (NIPD) is becoming increasingly popular for clinical and research applications. With rapid development, simplification of sample treatment procedures, improvement of data analysis protocol, and reduction in cost, genome sequencing technology will soon be available for common use in the laboratory and clinic. Sequencing technology will undoubtedly accelerate the progress of biomedical research, deepen the understanding of the pathogenesis of disease, promote the application of

personalized therapy, facilitate diagnosis and treatment of rare diseases, increase the opportunities for healthy birth, and improve the efficiency of disease diagnosis, prevention and treatment.

(7) Telemedicine

Telemedicine refers to the combination of medical science with the technology of remote communication, multimedia, data exchange and internet, which makes the remote acquisition, transmission, processing, storage and query of the various medical and health information possible, so as to realize detection, monitoring, diagnosis, information transmission and management of the remote object, and so on. Since the 1950s, telemedicine has developed from the initial voice communications realized at large medical centers for providing long distance medical information and services to poor and underdeveloped areas, into real-time interaction of interagency information, and significantly improved the accessibility and fairness of medical service. With the development of technology, the scope, form, efficiency and quality of telemedicine service continually improved. The key technical problems of telemedicine research in the current and upcoming period include those related to telemedicine information collection technology such as remote real-time rendering, intelligent speech recognition, use of remote check terminal and remote medical monitoring robots, safe reliable high-speed medical information transmission technology, data security technology of multi-source heterogeneous data interaction and integration, service platform, data processing and image reconstruction, management support technology of specialist processes, and quality specification. Telemedicine will continue to deepen the innovation and application in the areas of remote specialized diagnosis (e.g., ECG, imaging, pathology, and medical examination), clinical auxiliary diagnosis and treatment (e.g., remote consultation, outpatient service, operation guidance, medical services, etc.), health emergencies and disease emergency rescue, remote care, health management, intelligent decision support, remote medical education, remote medical surgery, information system, and platform construction, to usher in a profound technological revolution in traditional medical services.

(8) Precision drugs

Precision drugs refer to the small molecule drugs and biological drugs targeting specific molecules associated with a disease. With the development of omics technologies and bioinformatic tools, many biomarkers for specific diseases are identified based on analysis of big omics data from large samples. Some of them have been further evaluated as potential drug targets by investigating disease pathogenesis. Currently, small molecule inhibitors targeting intracellular kinases and monoclonal antibodies binding to cell membrane/extracellular proteins are widely used in clinical practice. With the development of technologies in drug discovery, application of machine learning and artificial intelligence would provide breakthrough tools for screening and designing small molecule drugs in addition to traditional methods such as virtual screening, structure-based drug design, and DNA-encoded compound library screening technology. Likewise, intelligent design and optimization platform based on antigen-antibody interaction patterns will promote the discovery of therapeutic antibodies compared to the current technologies used for antibody screening, humanization, and affinity maturation. In addition, establishment of animal models for human disease will also be essential for precision drug development. Collectively, application of rapid and efficient technologies will greatly improve the discovery of precision drugs for critical diseases such as cancer, autoimmune diseases, and inflammatory diseases, which would be of great significance for human health.

(9) Vaccine preparation

Vaccines are biological products used for preventing the occurrence and controlling the prevalence of infectious diseases via human-specific immune responses, namely, active immunity in terms of response to new antigens and passive immunity based on the presence of antibodies against "seen" antigens. The incidence rate of several infectious diseases have declined significantly due to the direct contribution of broad vaccination worldwide, e.g. vaccines for smallpox, poliomyelitis, measles, diphtheria, pertussis, hepatitis B, etc. Vaccine research and development in China made some critical breakthroughs during the past decade. Japanese encephalitis vaccine developed in China received WHO pre-certification in 2013, and the product has been exported to many developing countries in Asia. The comprehensive clinical trial of the Chinese recombinant Ebola vaccine was conducted in Africa in 2015, which marks a historic breakthrough for the Chinese vaccine industry. Nowadays,

the most challenging issue of global vaccine research and development is that the traditional methodology used in the development of inactivated vaccines, attenuated live vaccines, and other traditional vaccine, cannot be successfully used for generating vaccines against many infectious diseases, such as acquired immunodeficiency syndrome (AIDS) and dengue. Another issue is that the current processing methodologies for pathogen culture, separation, and purification cannot meet the needs of emergency vaccine manufacture. With the emergence of certain innovative vaccines such as subunit vaccines, viral vector vaccines, virus-like particle vaccines, and nucleic acid vaccines, and development of other cutting-edge technologies in vaccine development such as gene editing, synthetic biology, single-use bioreactors, advanced bio-manufacturing platform with process modularization and flexible factory, highly effective vaccine adjuvant, novel drug delivery system, and thermal stability technology, the efficiency of vaccine research and the manufacturing capacity of vaccines will improve significantly. Meanwhile all other sectors of global biopharmaceutical industry will also benefit from these technology progresses.

(10) Medical imaging techniques

With the development in informatics and medical imaging techniques, the importance of image analysis in clinical and scientific research has increased, which has led to immense progress in medical research and clinical treatment. Using serial digital image analysis and process techniques such as image enhancement, segmentation, registration, fusion and three-dimensional reconstruction, anatomic structures and diseased regions can now be localized, acquired, displayed in three dimensions, and quantified, which ensures the maximal utilization of medical imaging datasets. Certain developing perspectives include tomography image data analysis, 3-dimensional reconstruction model, tissue imaging techniques, holographic radiology diagnosis systems, big-data cloud process for medical images, magnetic interaction imaging devices, and so on. The above techniques are used in many fields, such as guided disease treatment (assisted surgery and imaging-guided radiotherapy) through rapid imaging process, establishment of radiomic or radio-genomic model, multi-modality molecular imaging and integrated traditional anatomic imaging, and new functional molecular imaging for extensively exploring the correlations between image information and disease biology information and prognosis, which would ensure accuracy in disease diagnosis and treatment.

2.2 Understanding of engineering development focus

2.2.1 Genome editing

The concept descriptions of genome editing has been mentioned in section 2.1 (1).

Genome editing applications take advantages of DNA repair mechanism triggered by site-specific double strand breaks (DSBs) to engineer a wide variety of genomic modifications as mentioned below: ① Gene knockout/deletion. This form of gene editing utilizes the error-prone nature of NHEJ to introduce small insertion-deletions (indels) at the target site, inducing frame-shift mutations in genes. It can be employed for disruption of disease-related genes or for establishment of disease models, etc. For example, generation of the CCR5 knockout via gene editing was employed to treat HIV infection. Gene editing at dual or multiple sites can simultaneously remove a designated fragment in order to activate or deactivate a gene of interest, such as excision of exons to restore the correct reading frame for a gene involved in Duchenne muscular dystrophy (DMD), or deletion of enhancer regions to treat hemoglobinopathies. ② Gene correction. This is used to correct disease-causing mutations in situ by promoting homology-directed recombination with an exogenous donor template. It has great potential in gene therapy of inherited diseases such as hemophilia. ③ Gene insertion. Exogenous genes are incorporated into the desired genomic site by genome editing, bypassing or alleviating risks of insertional mutagenesis due to random integration of viral vectors. In addition, targeted insertion of a normal copy of the defective gene into the endogenous locus theoretically enables physiological levels of expression. The capability of manipulating genomic sequences by genome editing has created numerous opportunities in medicine, agriculture, and the pharmaceutical industry. Gene editing strategies used for therapeutic purposes in clinical or preclinical applications are listed below: ① Anti-infectious diseases. The most common application is partially knocking out the genome of pathogens such as viruses, bacteria, etc. ② Cancer immunotherapy. Combining the CRISPR technology with CAR-T cell immunotherapy promises

to broaden the application of T-cell immunotherapy for diverse cancer types, and improve its safety aspects. Knockout of *PD-1* in T cells via gene editing increased T-cell effector function. ③ Treatment of hematological diseases. β-thalassemia was recovered at the molecular level by correcting the mutations in the hemoglobin-encoding sequence via gene editing-mediated ex vivo therapy. ④ Ocular disorders. Proof-of-principle studies suggest that deletion of an intronic region in *CEP290* via Cas9 gene editing restored substantial *CEP290* expression for the treatment of Leber congenital amaurosis (LCA). ⑤ Neuromuscular disorders. Recent studies demonstrated that deletion of one or more exons by CRISPR/Cas9 editing restored the expression of the dystrophin protein products in treatment of DMD. ⑥ Treatment of other disorders such as skin disorders, respiratory disorders, etc. In addition, genome editing technologies have exhibited extensive potentials in other fields. Genome editing-mediated genetic alteration in crops and animals may lead to remarkable increase in agricultural productivity and/or improve resistance to pathogens. In industry, numerous disease models can be established with high efficiency and less time using gene editing as the drug screening and evaluation platform. Genetically modified tools can be used competitively to augment industrial productivity. Based on the delivery methods, therapeutic genome editing strategies include ex vivo and in vivo therapy. In ex vivo therapy the target cells, such as somatic cells or hematopoietic stem cells (HSCs), are isolated from the patient, modified with the genome editing system, and subsequently returned to the host. This mode of treatment is likely to achieve higher editing efficiency with more flexible delivery methods under positive selection. Up till now, a number of clinical trials utilizing gene editing strategy have made breakthrough achievements, such as anti-HIV therapy. Moreover, combining the induced pluripotent stem cell (iPSC) technology with genome editing is very likely to have broader clinical applications. In vivo genome editing directly delivers the system into the host to target organs or tissues. The success of the in vivo therapy largely relies on the efficiency of the delivery vehicles. The main technical barrier is the divisional status of cells, which has an important effect on the system intake and editing efficiency. Lack of in vivo selection methods is also a drawback of the editing rate. So far, adeno-associated virus (AAV)-mediated Cas9 delivery has been demonstrated to be successful with specific tissue tropisms, such as to the liver and brain. Preclinical studies are currently under investigation using these methods.

At present, the primary challenges regarding clinical translation of genome editing are the safety concerns related to its off-target effects and the efficacy of the treatment. To address the safety issue, investigators optimize available systems to enhance targeting specificity; on the other hand, novel editing nucleases have been explored as alternative tools. The challenge to achieve efficient delivery needs to be solved by developing more accessible systems. Among a variety of viral vectors, the advantages of AAV vectors have gained remarkable attention and investments. In addition, non-biological vehicles such as nanoparticles might be a potent tool for delivering the editing system and should be optimized further. Genome editing has also attracted tremendous research interest in China. So far, the total number of the papers in this field published between 2011 and 2016 by Chinese investigators rank second worldwide. Therefore, further development should focus on discovering innovative technologies and promoting practical applications. In addition, ethical scrutiny and regulatory management are urgently required for appropriate application of the technology. The future of genome editing technology will depend on understanding of the current experience combined with systematic optimization and scientific planning.

In total, 231 core patents have been applied on genome editing methods within the past 5 years. The USA, Germany, France, Switzerland, and Japan rank as the top 5 countries with the most patents, and the USA is indeed in the leading according to the international collaboration network (Figure 2.2.1). Chinese authors have applied for 1.30% of the patents with an average citation frequency of 5 (Table 2.2.1).

The top 3 institutions with the maximum number of core patent inventors are the Broad Institute Inc., Massachusetts Institute of Technology, and Harvard College(Table 2.2.2), with the latter two institutions being the most productive. Furthermore, the collaboration network among international institutions(Figure 2.2.2) shows that there are active collaborations among various institutions, especially within the top three institutes.

Table 2.2.1 Major producing countries or regions of core patents on the engineering development focus "Genome editing"

No.	Country/Region	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	USA	217	93.94%	5277	97.18%	24.32
2	Germany	10	4.33%	212	3.90%	21.20
3	France	5	2.16%	38	0.70%	7.60
4	Switzerland	4	1.73%	40	0.74%	10.00
5	Japan	4	1.73%	60	1.10%	15.00
6	China	3	1.30%	15	0.28%	5.00
7	Canada	2	0.87%	4	0.07%	2.00
8	Denmark	2	0.87%	20	0.37%	10.00
9	Hungary	1	0.43%	9	0.17%	9.00

Table 2.2.2 Major producing institutions of core patents on the engineering development focus "Genome editing"

No.	Institution	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	Broad Inst Inc	102	44.16%	2946	54.25%	28.88
2	Massachusetts Inst Technology	102	44.16%	2946	54.25%	28.88
3	Harvard College	62	26.84%	1941	35.75%	31.31
4	Sangamo Biosciences Inc	32	13.85%	794	14.62%	24.81
5	Sigma-Aldrich Co Llc	14	6.06%	447	8.23%	31.93
6	Factor Bioscience Inc	8	3.46%	352	6.48%	44.00
7	Univ Rockefeller	8	3.46%	425	7.83%	53.13
8	Pioneer Hi-Bred Int Inc	7	3.03%	37	0.68%	5.29
9	Editas Medicine Inc	7	3.03%	118	2.17%	16.86
10	Pioneer Int Co Ltd	6	2.60%	36	0.66%	6.00

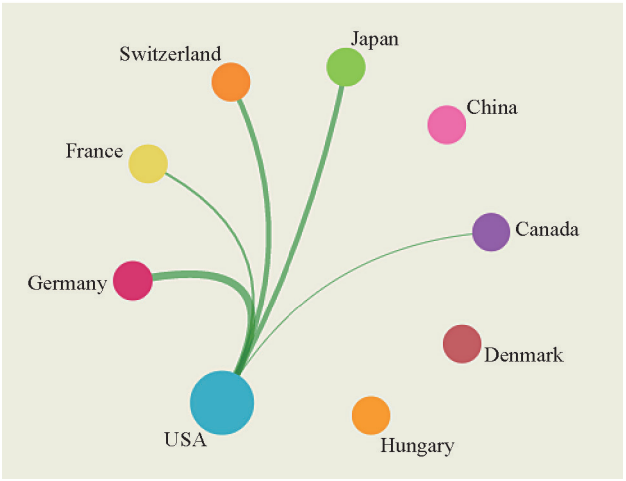

Figure 2.2.1 Collaboration network of the major producing countries or regions of core patents on the engineering development focus "Genome editing"

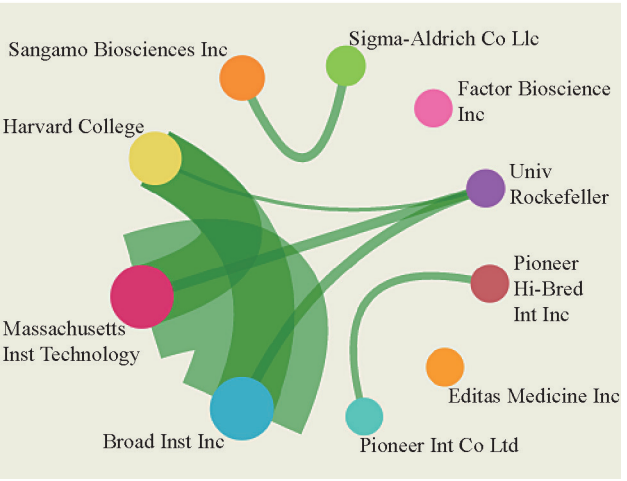

Figure 2.2.2 Collaboration network of the major producing institutions of core patents on the engineering development focus "Genome editing"

2.2.2 Immune cell therapy

The concept descriptions of immune cell therapy has been mentioned in section 2.1 (2).

The key technical problems of immune cell therapy include: ① Enhanced targeting to guide lymphocytes to tumor tissues precisely and efficiently. Developing more accurate and efficient living cell genetic modification techniques based on chimeric antigen receptor (CAR) γ δ T cells or natural killer cells (NK cells) (e.g., by using genetic engineering technique, we can produce T cells modified with monoclonal antibody against tumor-specific antigen linked to TCR receptor, CAR-T, or NK cells modified with tumor-specific monoclonal antibody linked to NK cell receptor NKG2D, CAR-NK) and antibody-arming technique (a technique that conjugates the monoclonal antibody with the toxins, which can direct the toxins to tumor cells through specific identification of tumor antigen by antibody and kill them). Currently, there are still a handful of tumor-specific targets and their corresponding targeting approaches available, which becomes the global focused competition. ② Large-scale expansion of lymphocytes. Owing to the limited number and short shelf-life of lymphocytes isolated from patient blood, obtaining a sufficient amount of effective lymphocytes is a key problem of this technology. So far, using an ordered combination of cytokines and co-stimulatory factors, sufficient amounts of immune cells such as cytokine-induced killer cells (CIK), cytotoxic T lymphocytes (CTL), NK cells, γ δ T cells, and dendritic cells (DC) can be obtained for clinical applications, which could be applied to different tumor types or patients. These immune cells can not only be directly infused into cancer patients, but also be genetically modified for developing cancer killer cells with precise targeting capabilities. However, limitations in several technical aspects, including the expansion efficiency of different types of immune cells in vitro, the amount of specific effector cells required, and the survival states of these cells in the human body after the infusion, still exist. Therefore, more systematic and standard specifications for researches in this field are needed. The most notable CAR-T technology involves the combination of the two above-mentioned techniques (large-scale expansion and CAR genetic modification), which presents encouraging efficacy in the treatment of hematological malignancies in clinical trials. CAR-T cells targeting various solid tumors have also entered clinical trials. In 2014, CAR-T was designated a "breakthrough therapy" by the FDA of USA. Currently, there are 241 CAR-T clinical trials registered on clinicaltrials.gov in the world, and among them, the top three contributing countries are the USA (113), China (99), and Europe (24), respectively. ③ Establish standard operating procedures of cellular immunotherapy. Owing to the individualization of operation, this technology has not been applied in large-scale production and used as conventional drugs. Therefore, it is necessary to establish a unified operating standard and a quality control system for effective use of this technology. Cell immune therapy in China started relatively late compared to other countries; however, it is now an emerging industry, and has been listed as one of the key research projects supported by the national policy. With the gradual standardization and improvement of China's industrial policy on immune cell therapy, as well as the entry of well-known international enterprises, the potential for the development of the industry will be released, and research and development regarding the clinical applications of this industry will develop faster.

There are 654 core patents for "Immune cell therapy technology" (Table 2.1.1) and the top five contributing countries are the USA, Germany, China, Switzerland, and France. Among them, the patents applied by Chinese authors accounted for 10.09%, and the proportion of the number of patents is large. China has become one of the key research countries of this focus of engineering development with the average citation frequency of 28.06(Table 2.2.3). As shown in the cooperation network of patent-producing countries (Figure 2.2.3), the United States, China and Switzerland cooperate more closely.

The top three institutions of the core patent output are Moderna Therapeutics, Atyr Pharma Inc and the University of Pennsylvania (Table 2.2.4), which are mainly biotech companies and universities. According to the cooperation network (Figure 2.2.4) between the major institutions, there is more collaboration between major output institutions developing the focused patent technology.

The closest cooperation is mainly between Atyr Pharma Inc and Pangu Biopharma Ltd companies, Novartis and the University of Pennsylvania, drug companies and research institutions of university, as well as Bayer and Curevac Gmbh companies.

Table 2.2.3 Major producing countries or regions of core patents on the engineering development focus "Immune cell therapy technology"

No.	Country/Region	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	USA	487	74.46%	12 342	76.71%	25.34
2	Germany	73	11.16%	2 471	15.36%	33.85
3	China	66	10.09%	1 852	11.51%	28.06
4	Switzerland	50	7.65%	1 296	8.05%	25.92
5	France	30	4.59%	440	2.73%	14.67
6	Canada	10	1.53%	141	0.88%	14.10
7	UK	10	1.53%	86	0.53%	8.60
8	India	10	1.53%	73	0.45%	7.30
9	Sweden	7	1.07%	154	0.96%	22.00
10	Belgium	6	0.92%	147	0.91%	24.50

Table 2.2.4 Major producing institutions of core patents on the engineering development focus "Immune cell therapy technology"

No.	Institution	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	Moderna Therapeutics	55	8.41%	1646	10.23%	29.93
2	Atyr Pharma Inc	48	7.34%	1992	12.38%	41.50
3	Univ Pennsylvania	43	6.57%	1213	7.54%	28.21
4	Pangu Biopharma Ltd	40	6.12%	1544	9.60%	38.60
5	Hutchinson Cancer Res Cent Fred	35	5.35%	537	3.34%	15.34
6	Novartis Ag	34	5.20%	1052	6.54%	30.94
7	Curevac Gmbh	29	4.43%	1520	9.45%	52.41
8	Bayer Intellectual Property Gmbh	26	3.98%	709	4.41%	27.27
9	Cellectis	22	3.36%	397	2.47%	18.05
10	Ibc Pharm Inc	22	3.36%	506	3.14%	23.00

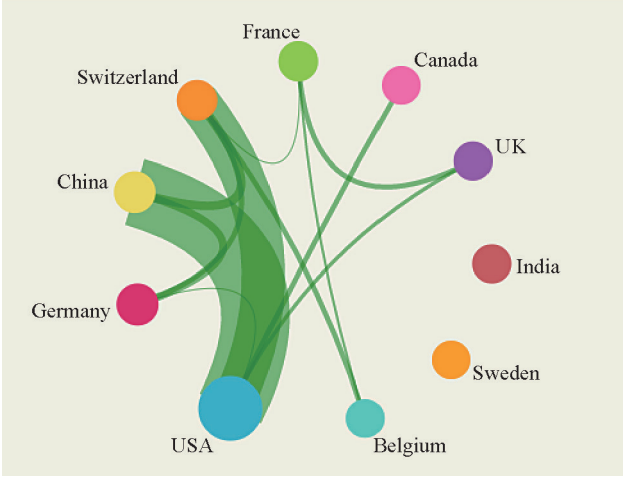

Figure 2.2.3 Collaboration network of the major producing countries or regions of core patents on the engineering development focus "Immune cell therapy technology"

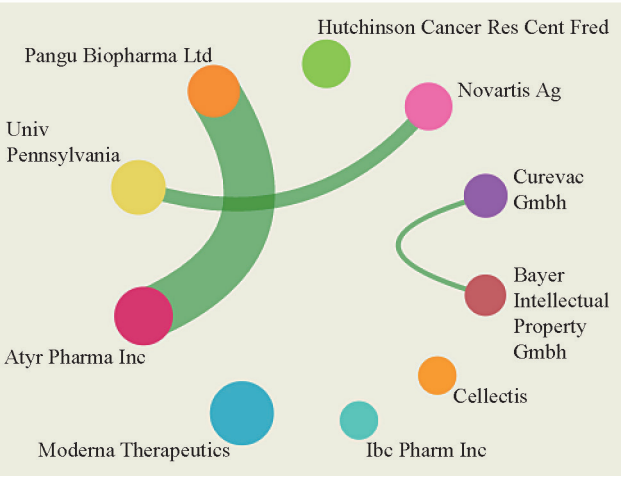

Figure 2.2.4 Collaboration network of the major producing institutions of core patents on the engineering development focus "Immune cell therapy technology"

2.2.3 Stem cell technology

The concept descriptions of stem cell technology has been mentioned in section 2.1 (3).

Although stem cell research has progressed immensely in recent years, certain critical technologies should be further developed for better understanding and clinical applications of stem cells: ① Establishment of robust, clinical-grade culture methods for culturing stem cells in vitro, methods for maintenance of pluripotency, especially the ground state of pluripotent stem cells, and deciphering the underlying mechanisms, optimization of in vitro reprogramming methods, identification of pluripotent stem cell-specific surface antigens and transcription factors, exploration of mechanisms underlying exit from pluripotency, lineage differentiation, and potential risks of tumor formation. ② Clinical-grade methods for isolation and culture of the adult (tissue) stem cells. Since the adult stem cells are heterogeneous in nature and their surface markers are not fully defined, current methods for long-term growth and expansion of self-renewing adult stem cells remain largely unsuccessful. ③ Directed differentiation of pluripotent stem cells. Specific tissues or cells can be derived from PSCs by addition of growth factors or drugs, which harness their pluripotency, e.g. islet β cells, endothelial cells, and hematopoietic stem cells, etc. ④ Transdifferentiation. Mature somatic cells can be converted into other cell types by ectopic expression of certain genes or induction by certain small molecules. Latest reports also show that transdifferentiation can occur in situ by converting cells within the damaged tissues into cells of interest for further treatment. ⑤ Engineering of complex structures in vitro. Stem cells can self-organize into organoid structures supported by certain biomaterials in three-dimensional culture. These organoids can recapitulate functions and structures of normal tissues and organs, which lay the foundation for future transplantation of artificial tissues and organs. ⑥ Methods for genetic and epigenetic manipulations of stem cells. Stem cells are characterized by unique biological traits. Cutting-edge methods such as genome editing and stem cell transfection can be adopted for manipulation of stem cell fate and gene therapy, which have enormous potential for clinical applications. China has demonstrated steady growth in stem cell research and development in the past few years, while western countries like the USA remain the major players in the global stem cell industry. Stem cell industry in China is still at the incipient stage, with most of the companies focused on the upstream industry, mainly on biobanking.

The core patents related to engineering and research focus in stem cell technologies amount to 1173 (Table 2.1.1), and the top 5 countries are the USA, China, Germany, Switzerland, and Japan. Among all countries, China contributes 12.45% authors applying for patents; China also occupies a comparatively large proportion in the sheer volume of patents, and it has become one of the most important countries in this area, with an average citation frequency of 14.14 (Table 2.2.5). The cooperative network among countries with patent output in this area (Figure 2.2.5) show the USA and China to be most cooperative.

The top three institutions with core patent output are Anthrogenesis Corp., Atyr Pharma Inc., and the Massachusetts Institute of Technology (MIT) (Table 2.2.6). Institutions with core patent output are mainly biotechnology corporations and universities. China is less industrialized compared to the innovative pattern of patent output driven by corporations. The cooperative network among major institutions (Figure 2.2.6) shows that the connections between major institutions in this focus area are relatively weak, whereas among all, the MIT, the General Hospital Corporation, and the Massachusetts General Hospital show cooperative ties in research and development.

2.2.4 Biomedical materials

The concept descriptions of biomedical materials has been mentioned in section 2.1 (4).

The current hotspots in the field of international medical materials research include the following: ① Biodegradable materials that can be gradually degraded or metabolized after being implanted in the human body with time. The foreign body implanted will automatically degrade into non-toxic, harmless substances that can be expelled from the body after completion of the mission. ② Tissue engineering materials and artificial organs to construct biological devices by using engineering principles and methods. These would to replace the damaged tissues or organs, and include the use of biological scaffolds, seed cells, and growth factors to establish complex three-dimensional spaces composed of cells and biological materials. It is imperative to develop biological materials with good biocompatibility and ability to gradually degrade and be assimilated by

Table 2.2.5 Major producing countries or regions of core patents on the engineering development focus "Stem cell technologies"

No.	Country/Region	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	USA	764	65.13%	15 846	75.41%	20.74
2	China	146	12.45%	2 064	9.82%	14.14
3	Germany	63	5.37%	1 070	5.09%	16.98
4	Switzerland	52	4.43%	1 394	6.63%	26.81
5	Japan	46	3.92%	567	2.70%	12.33
6	Korea	42	3.58%	501	2.38%	11.93
7	Canada	32	2.73%	641	3.05%	20.03
8	Singapore	25	2.13%	490	2.33%	19.60
9	France	20	1.71%	289	1.38%	14.45
10	UK	16	1.36%	276	1.31%	17.25

Table 2.2.6 Major producing institutions of core patents on the engineering development focus "Stem cell technologies"

No.	Institution	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	Anthrogenesis Corp	33	2.81%	419	1.99%	12.70
2	Atyr Pharma Inc	32	2.73%	1248	5.94%	39.00
3	Massachusetts Inst Technology	29	2.47%	454	2.16%	15.66
4	Pangu Biopharma Ltd	28	2.39%	1096	5.22%	39.14
5	Harvard College	25	2.13%	585	2.78%	23.40
6	Moderna Therapeutics	20	1.71%	912	4.34%	45.60
7	Sangamo Biosciences Inc	19	1.62%	486	2.31%	25.58
8	The General Hospital Corporation Dba Massachusetts General Hospita	17	1.45%	258	1.23%	15.18
9	Hoffmann La Roche Inc	17	1.45%	335	1.59%	19.71
10	Oncomed Pharm Inc	14	1.19%	192	0.91%	13.71

human bodies. These are used mainly to develop artificial blood, liver, heart, kidney, pancreas, blood vessel, cornea cerebrovascular stents, etc. ③ Materials for tissue engineering bones and cartilages to repair defective bones and joints using engineering principles. Electrospinning technology is used on bones, cartilages, and adipose tissue stem cells to develop artificial bone, cartilage knee joints, hip joints, meniscus, ligament, muscles, etc. ④ Dental restorative materials for developing biomaterials for the restoration of maxillofacial, mandibular, and tooth defects. ⑤ Controlled release materials for the release of drugs at a constant rate over a certain period of time. Materials are divided into natural and synthetic polymer materials. ⑥ Bionic intelligent materials: These materials are designed on the principle of synergistic interaction among biological macromolecules to produce intelligent materials with the desired host response. They imitate the cooperative behavior of biomedical materials. ⑦ Antibacterial membrane biomaterials form a biofilm on the surface of implant materials to prevent bacterial growth in postoperative infections. Since post-operative clinical bacterial film infections occur in 2%-3% cases, there is a huge market for these materials. ⑧ Nano biomedical materials, is a new interdisciplinary field regarding the structure and function of genes and proteins, including their identification, integration, transformation, special factor release, bioelectrochemical signal generation and conduction, and biomechanical and thermodynamic

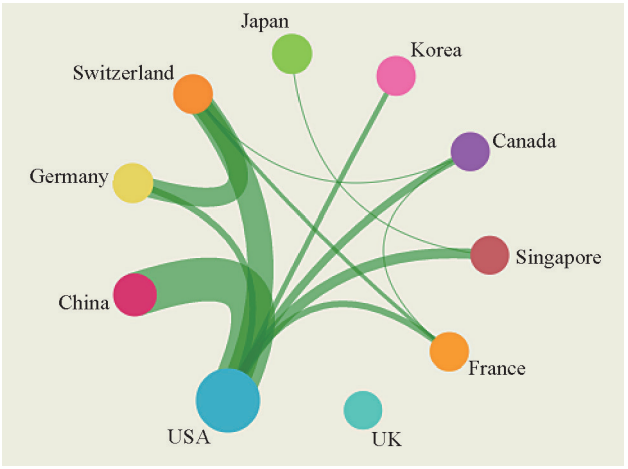

Figure 2.2.5 Collaboration network of the major producing countries or regions of core patents on the engineering development focus "Stem cell technologies"

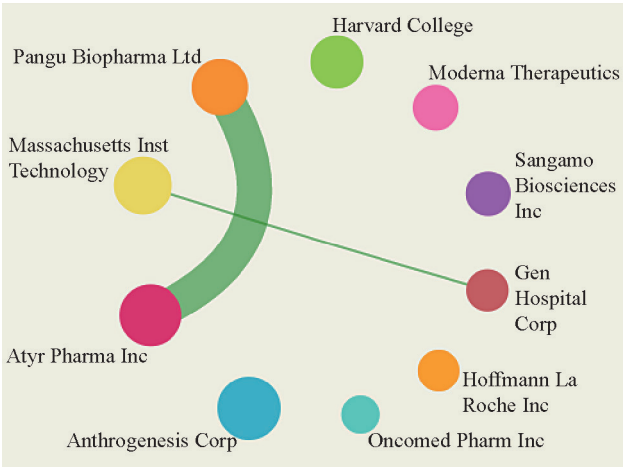

Figure 2.2.6 Collaboration network of the major producing institutions of core patents on the engineering development focus "Stem cell technologies"

properties. It also involves the development of new technical tools using multidisciplinary research.

The market demand for biomedical materials is enormous. In the past 10 years, it has been increasing at an annual rate of 20%, reaching $130 billion in 2013 and $220 billion in 2016. The USA and other western countries occupy the high end market of biomedical materials, whereas the biomedical materials market share of China is 6.5% of its domestic market. Thus, biomedical materials constitute products of the low-end market.

In total, 191 core patents have been applied on biomedical materials in the past 5 years. The USA, China, Korea, the UK, and Italy are ranked as the top 5 countries with the most patents in force (Table 2.2.7). The patents applied by Chinese authors accounted for 21.99% of the total patents and the proportion of the number of patents is large (Table 2.2.7). China has become one of the key countries researching on this aspect of engineering development with an average cited frequency of 10.02. As shown in the cooperation network of patent-producing countries (Figure 2.2.7), the United States and Italy, UK and France cooperate more closely.

The top 3 institutions with the most inventors of the core patents in force are Tufts College, Optotrace Technologies, and Ajou University (Table 2.2.8). Besides, the collaboration network among international institutions shows that the cooperation of biomedical materials is few (Figure 2.2.8).

Table 2.2.7 Major producing countries or regions of core patents on the engineering development focus "Biomedical materials"

No.	Country/Region	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	USA	104	54.45%	2128	68.10%	20.46
2	China	42	21.99%	421	13.47%	10.02
3	Korea	13	6.81%	229	7.33%	17.62
4	UK	10	5.24%	132	4.22%	13.20
5	Italy	5	2.62%	86	2.75%	17.20
6	Australia	4	2.09%	80	2.56%	20.00
7	Switzerland	4	2.09%	90	2.88%	22.50
8	France	4	2.09%	38	1.22%	9.50
9	Canada	3	1.57%	5	0.16%	1.67
10	Germany	3	1.57%	5	0.16%	1.67

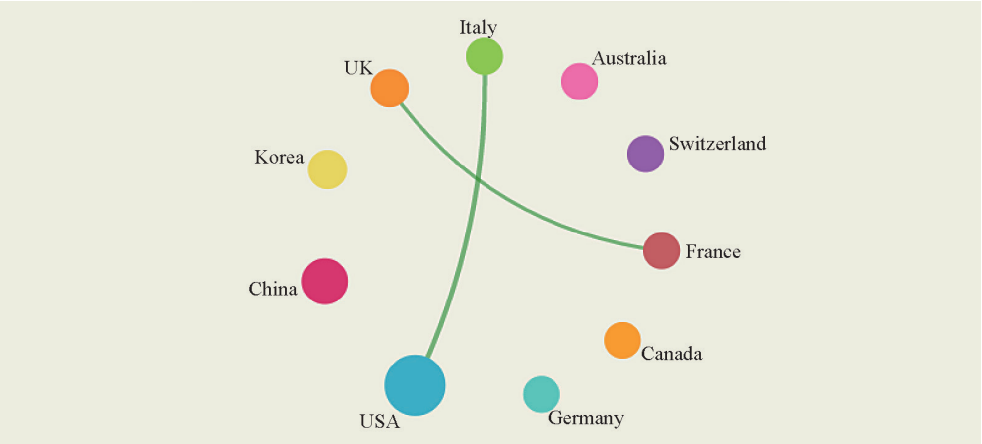

Figure 2.2.7 Collaboration network of the major producing countries or regions of core patents on the engineering development focus "Biomedical materials"

Table 2.2.8 Major producing institutions of core patents on the engineering development focus "Biomedical materials"

No.	Institution	Published patents	Proportion of published patents	Citation frequency	Proportion of citation frequency	Average citation frequency
1	Tufts College	18	9.42%	384	12.29%	21.33
2	Optotrace Technologies	10	5.24%	225	7.20%	22.50
3	Ajou University	9	4.71%	145	4.64%	16.11
4	Allergan Inc	8	4.19%	261	8.35%	32.63
5	Massachusetts Inst Technology	6	3.14%	82	2.62%	13.67
6	Smith & Nephew Plc	6	3.14%	63	2.02%	10.50
7	Univ Johns Hopkins	5	2.62%	190	6.08%	38.00
8	Depuy Prod Inc	4	2.09%	107	3.42%	26.75
9	Univ Monash	4	2.09%	80	2.56%	20.00
10	Univ Kyungpook Nat Ind Acad Coop	4	2.09%	84	2.69%	21.00

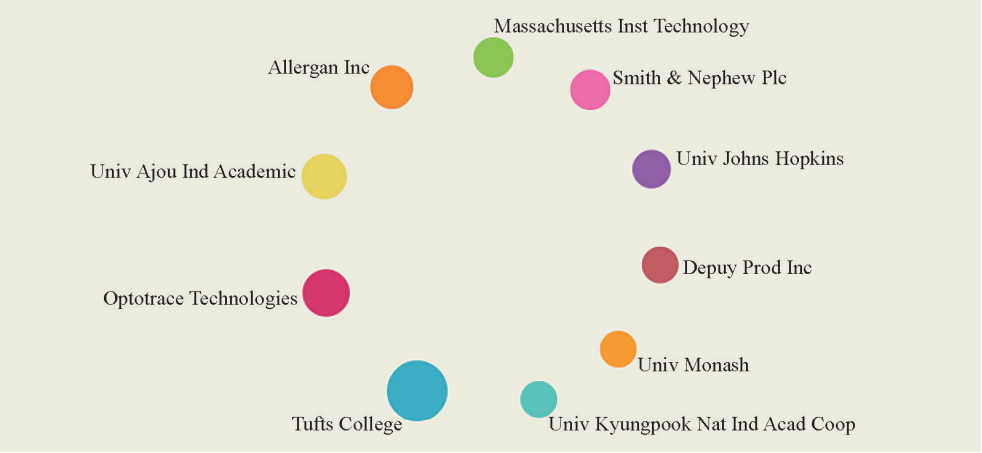

Figure 2.2.8 Collaboration network of the major producing institutions of core patents on the engineering development focus "Biomedical materials"

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