VIII. Medicine and Health

1 Engineering research fronts

1.1 Trends in top 10 engineering research fronts

This review describes the top 10 engineering research fronts in the field of medicine and health, which includes the areas of basic medicine, clinical medicine, medical informatics and biomedical engineering, pharmacy, public health, and preventive medicine. These 10 fronts are "artificial intelligence (AI) in biomedicine," "gut microbiota and immune homeostasis," "neural computation and brain-inspired intelligence in the brain sciences," "organoids-on-a-chip and its biomedical applications," "tumor immunotherapy," "personalized tumor therapeutic vaccines," "application of stem cells in regenerative medicine," "metabolic heterogeneity and interactions in tumor microenvironments," "precise diagnosis of diseases based on single-cell sequencing," and "application and research of 3D printing technology in regenerative medicine" (Table 1.1.1). The numbers of core papers on these frontiers published between 2014 and 2018 are listed in Table 1.1.2.

(1) AI in biomedicine

AI is a technical science used to simulate and extend the theory, methods, techniques, and applications of human intelligence. The application of AI in biomedicine can increase accuracy and safety in a range of biomedical fields, such as health screening and warning, disease diagnosis and treatment, rehabilitation training and evaluation, medical services and management, drug screening and evaluation, and gene sequencing and characterization. These fields are all driven by medical data, including images, atlases, medical records, and other medical information sources, which can be processed by AI in various applications. For example, in health screening and warning, these applications include disease screening, chronic disease management, and wearable health monitoring devices. In disease diagnosis and treatment, AI can be applied to automatic lesion recognition, intelligent treatment decision-making, scientific evaluation of curative effects, robotic assisted surgery, and remote surgery. Rehabilitation training and evaluation applications involve cognitive impairment rehabilitation, disability and rehabilitation, robotic care, intelligent prostheses, and orthoses (including assistive exoskeleton devices). Applications in medical services and management include electronic medical record management, intelligent automatic drug delivery, and medical Internet of Things (IoT) services. Drug screening and evaluation can utilize AI in drug target identification, drug screening, drug efficacy tests, drug

Table 1.1.1 Top 10 engineering research fronts in medicine and health

No.	Engineering research front	Core papers	Citations	Citations per paper	Mean year
1	AI in biomedicine	670	33 946	50.67	2015.4
2	Gut microbiota and immune homeostasis	63	7 550	119.84	2015.1
3	Neural computation and brain-inspired intelligence in the brain sciences	300	21 173	70.58	2015.3
4	Organoids-on-a-chip and its biomedical applications	20	2 111	105.55	2016.2
5	Tumor immunotherapy	610	159 484	261.45	2015.4
6	Personalized tumor therapeutic vaccines	139	12 063	86.78	2016.1
7	Application of stem cells in regenerative medicine	957	62 555	65.37	2014.9
8	Metabolic heterogeneity and interactions in tumor microenvironments	123	10 501	85.37	2015.4
9	Precise diagnosis of diseases based on single-cell sequencing	32	6 782	211.94	2015.6
10	Application and research of 3D printing technology in regenerative medicine	208	14 259	68.55	2015.4

Table 1.1.2 Annual number of core papers published for the top 10 engineering research fronts in medicine and health

No.	Engineering research front	2014	2015	2016	2017	2018
1	AI in biomedicine	222	165	135	102	46
2	Gut microbiota and immune homeostasis	27	12	17	6	1
3	Neural computation and brain-inspired intelligence in the brain sciences	98	80	60	48	14
4	Organoids-on-a-chip and its biomedical applications	1	3	10	4	2
5	Tumor immunotherapy	189	157	127	99	38
6	Personalized tumor therapeutic vaccines	9	32	49	34	15
7	Application of stem cells in regenerative medicine	414	276	181	81	5
8	Metabolic heterogeneity and interactions in tumor microenvironments	36	29	36	19	3
9	Precise diagnosis of diseases based on single-cell sequencing	9	8	5	7	3
10	Application and research of 3D printing technology in regenerative medicine	35	84	58	30	1

safety evaluation, and adverse reaction data management. Finally, applications in the field of gene sequencing and characterization include gene screening, genome sequencing, gene editing, and individualized medical treatment. The application of AI in biomedicine is changing the approach of modern biomedical development. On the one hand, AI can benefit the whole medical process, including intelligent management of disease pathogenesis, precise diagnosis, safe treatment, and scientific evaluation. This has the result of significantly improving the professional efficiency of doctors, alleviating the shortage of doctors, improving the accuracy of diagnosis and treatment, and optimizing the allocation of high-quality medical resources. On the other hand, AI systems can enable real-time health monitoring and warning, and the rapid development of medical IoT, medical health hardware, and wearable health devices. Overall, the application of AI in biomedicine can aid innovation in medical technology and enable healthcare to progress to a new stage of quantitative analysis.

(2) Gut microbiota and immune homeostasis

The discovery of the important physiological function of human microbiota has subverted our understanding of human health and survival. In recent years, multiple studies have revealed the scale and complexity of microbial communities inhabiting the body surface and coelomic cavities of humans (over 10^{14} cells of bacteria, archaea, fungi, and viruses, dry weight approximately 1%–2% of the total human body weight). These microbes colonize areas such as the gastrointestinal tract, oral cavity, skin, and urogenital tract. As these organisms contain 50–100 times more genes than the human body and encode a myriad of important biological processes, their genome is regarded as the “second genome” of the human body. These microorganisms and their living environment constitute human microbiota, which perform essential physiological functions over the course of human life. By directly or indirectly regulating the functions of the liver, digestive system, immune system, nervous system, and brain, they provide important maintenance of digestion, absorption, immune response, and material and energy metabolism, affecting human development, growth, health, and aging. This subverts the traditional concept of humans functioning as an independent species and opens the new concept of a mutually beneficial coexistence of human beings and microorganisms.

Nearly 80% of human microorganisms are located in the intestinal tract, forming the intestinal microbiota. Intestinal microbiota plays a significant role in disease by significantly affecting the processes of early warning, prevention, diagnosis, treatment, and rehabilitation. In recent years, multiple studies have identified key roles of intestinal microbiota in infections, liver diseases, metabolic diseases, autoimmune diseases, tumors, and brain and neuropsychiatric diseases. This has become a breakthrough for understanding the pathogenesis of major diseases. Research into important pathogenic microorganisms and alterations in intestinal microbiota before the occurrence of disease has opened a new chapter in disease prevention and early warning. New diagnostic methods based on intestinal microbiota alterations will not only become necessary tools for the diagnosis of unexplained and sudden infections, but will also be key for identifying and predicting the complex course of particular diseases, such as cirrhosis and hepatocellular carcinoma. Most chronic diseases are related to inflammation, and the intestine is one of the largest immune organs in the human body. The distribution of immune cells and the production of inflammatory factors can affect the occurrence and development of chronic diseases through direct or indirect contact with intestinal microorganisms and their metabolites. Metabolites of intestinal microorganisms have also been shown to affect the expression and regulation of intestinal inflammatory signals. Therefore, clarifying the interactions between the immune system, intestinal microorganisms, and microbial metabolism is of great significance for the prevention, intervention, and treatment of chronic diseases. The efficacy of most oral and injected drugs is closely related to the composition and function of intestinal microbiota. Relevant assessment of gut microbiota to prescribe accurate treatment could be highly significant for improving disease therapy and saving medical expenses. As well as its importance in directly or indirectly treating infections, liver diseases, metabolic diseases, autoimmune diseases, and tumors, gut microbiota regulation can overcome health problems that result from microbiota damage caused by the occurrence, development, and treatment of most diseases.

(3) Neural computation and brain-inspired intelligence in the brain sciences

Neural computation and brain-inspired intelligence in the brain sciences is a multidisciplinary field incorporating neuroscience and mathematics. It is a new research field that involves theories and analytical methods of mathematics, computer science, neuroscience, biology, physics, cognitive psychology, social and behavioral science, and engineering. It also involves the analysis of big data, including genetics, neurons, neuroimaging, large-scale cognitive functions, and the environment, in multiple dimensions across time and space. In order to investigate mechanisms and dynamics of neural systems, decipher the principles of information processing/neural coding in the brain, and decode the mechanisms of brain function, the field incorporates methods such as quantitative analysis, computational models, and brain-inspired computation. The ultimate aim of the field is to use information technology to simulate higher functions of the brain and develop brain-inspired algorithms in order to establish new fields, such as novel models and algorithms of AI, brain-inspired chips, and brain-inspired engineering technology. In this way, this emerging field embodies the quote that ‘brain-inspired intelligence leads the development of artificial intelligence’.

Research of neural computation and brain-inspired intelligence in the brain sciences has two aspects: First, it involves neurobiological research into the essence of brain computation; second, it uses computational methods to decode the principles of brain intelligence, in order to create new technologies that cover several areas related to AI. Currently, AI, as represented by deep learning is rapidly changing methods of production and consumption. The products and models derived from it have been primarily applied to the Internet, software, digital business, cloud computing, healthcare, and industrial manufacturing. Taking industrial manufacturing as an example, the wave of digitalization is accelerating the development of industry globally. For example, Industry 4.0 in Germany employs algorithms and chips that enable the entire production process to independently perceive, learn, and make improvements, leading to a more flexible and individualized synthetic processes. According to a report published by Deloitte, the global market of AI may increase to 6 trillion USD by 2025. The next generation of AI, led by brain-inspired intelligence, provides very important and far-reaching opportunities. It has the potential to transform traditional industries, including healthcare, consumption, urban management, and industrial manufacturing, revolutionize their development, and potentially exert massive economic and social impact. Moreover, the field will also affect military security, information security, biological security, information analysis, and many other important areas.

(4) Organoids-on-a-chip and its biomedical applications

Organoids-on-a-chip, a recently proposed three-dimensional (3D) culture platform, aims to integrate pluripotent cell culture with microfluidic chips *in vitro*. By simulating and controlling the biological behaviors of cell clusters, the spatial structures of their tissue source can be recapitulated, and their crucial functions can be reproduced on the chip. Due to its high structural comparability and functional consistency, the organoids-on-a-chip approach exhibits enormous potential in drug screening and evaluation, genetic disease modeling, cell therapy, and various other biomedical applications. Although organoids-on-a-chip research is still in the initial stages, it has been highly regarded as a catalyst for the rapid development of translational medicine owing to its possibilities for multi-organ integration and high bio-functional simulation. To realize its potential, several vital scientific issues need to be resolved, including expansion of the cell or tissue sources, exploration of the co-culture system, substitutes for extracellular matrix (ECM), design of integrated chip systems, control of the inner microenvironment, and integration of multiple functions or organs. As for the current status of the field, western research institutes and biotechnology companies are promoting the development of related technologies, and have already dominated some important technological patents. Moreover, the US Food and Drug Administration (FDA) has announced that they are comparing experimental results from organoids-on-a-chip with those from animal models, and the results will be used to verify the feasibility of replacing current *in vivo* methods with organoids-on-a-chip. As an important trend in new drug evaluation systems, the organoids-on-a-chip field has great strategic significance for supporting the national drug research and translational medicine innovation. Despite the remarkable achievements to date, the organoids-on-a-chip field further aims to solve challenges in the areas of physiological-chip-system construction, multi-organ functional association and synergy, sensing integration, and detection standardization. These aims will therefore become the focal development direction of the organoids-on-a-chip field in the future.

(5) Tumor immunotherapy

Tumor immunotherapy is a method used to monitor and eliminate tumor cells by reactivating the specific immune response to the tumor and restoring the normal activity of the anti-tumor immune system. The main methods used in tumor immunotherapy are immune checkpoint inhibitors, adoptive immunotherapy, neoantigen vaccines, and small molecule inhibitors. The prospects for application of tumor immunotherapy, in particular the immunological checkpoint inhibitors PD-1/PD-L1, are highly anticipated. The current key issues for tumor immunotherapy are as follows: 1) The serious adverse reactions of immunotherapy and the mechanism of accelerated progression are unclear; 2) The predictive biomarkers of immunotherapy efficacy are uncertain; 3) The efficacy of combined immunotherapy should be further improved; and 4) Resistance mechanisms and relevant solutions need to be analyzed. Following the development of oncological immunology, tumor immunotherapy has developed as a novel method of cancer treatment, with comparable significance to the traditional methods of surgery, radiotherapy, and chemotherapy. The theme of the 2017 annual progress report of the American Society of Clinical Oncology (ASCO) was “precision and alliance: immunotherapy 2.0,” marking the arrival of the 2.0 era of immunotherapy. Furthermore, the 2018 Nobel Prize in Physiology or Medicine was awarded to two professors of immunotherapy, Professor James Allison and Professor Tasuku Honjo, for their pioneering research on tumor immunotherapy. “Immunotherapy 2.0” has three characteristics: continuously expanding indications, seeking targeted beneficiaries, and obvious trend of combined therapy. At present, tumor immunotherapy has made considerable breakthroughs in the treatment of malignant tumors such as melanoma, ovarian cancer, colorectal cancer, and lung cancer. Immunotherapy, when combined with surgery, radiotherapy, chemotherapy, and other treatments, can significantly improve the survival of patients with malignant tumors, presenting major advantages over conventional radiotherapy and chemotherapy in practice. At present, China has established a relatively complete tumor immune drug research and development (R&D) program, and many domestic original immune checkpoint inhibitors have been marketed. In the field of tumor immunotherapy, in particular the clinical development of original immunotherapy drugs, China is on a par with the developed countries.

(6) Personalized tumor therapeutic vaccines

Personalized tumor therapeutic vaccines are therapeutic vaccines based on specific carcinogenic neoantigens. Neoantigens usually confer strong immunogenicity *in vivo* as they are produced due to specific gene mutations in tumor cells and are distinct from autogenic antigens that are normally tolerated by the central immune system. Therefore, the administration of neoantigens can overcome the immune suppression caused by tumors and activate tumor-specific immune cells, consequently controlling or eliminating the tumor. Since the gene mutations and neoantigens are specific to each tumor, it is necessary to produce neoantigen-based therapeutic vaccine in a personalized manner. The development of a personalized tumor therapeutic vaccine involves screening potent neoantigens, and applying algorithms to predict the binding affinity between neoantigen and human leukocyte antigen (HLA). Tumor therapeutic vaccines have been investigated for almost 20 years. However, early tumor therapeutic vaccines, which used tumor-associated antigens (TAA) as their major constituent, did not sufficiently stimulate the immune system to recognize and eliminate tumor cells, due at least partly to the pre-existence of immune tolerance. However, recent advances in next-generation sequencing (NGS) and bioinformatics have allowed a systematic discovery of carcinogenic neoantigens. In July 2017, the results of two separate clinical trials were simultaneously published by *Nature*, both ushering the dramatic advance of tumor therapeutic vaccine development. The two research teams applied high-throughput second-generation sequencing technology to identify the specific gene mutations in rapidly-dividing tumor cells, used specific algorithms to select targets with strong affinity for HLA, and generated peptide or mRNA vaccines for immunotherapy. The resulting vaccines have demonstrated excellent clinical effects and attracted great public attention. At present, a number of Chinese R&D institutions and enterprises engage in the area of personalized tumor therapeutic vaccines. In the future, the main trends for the development of personalized tumor therapeutic vaccines will be to decipher tumor immune mechanism, optimize the algorithm of screening new antigens, develop preclinical tumor models, shorten the production cycle of vaccines, and develop combinatory therapy strategies.

(7) Application of stem cells in regenerative medicine

Regenerative medicine aims to repair pathological or damaged cells, tissues, or organs, primarily via the use of seed cells, in particular stem cells. Stem cells are a unique cell type that possess the ability for self-renewal and multilineage differentiation. They can currently be divided into two categories according to their functions in the field of regenerative medicine: pluripotent stem cells, which include embryonic stem cells and induced pluripotent stem cells; and somatic stem cells, which include, for example, hematopoietic stem cells, mesenchymal stem cells, and neural stem cells. The key scientific issues of regenerative medicine include effective scaling and quality control of stem cells, efficiently differentiating pluripotent stem cells into targeted functional cells, activating stem cells *in vivo* for tissue regeneration, and constructing 3D tissues by combining stem cells with biomaterials. In addition, there is a lack of standardization in several aspects of the field, including the safety and effectiveness of stem cell treatments combined with gene therapy, particularly for hereditary diseases, the evaluation of the effectiveness of multi-stem cell-based treatment of tissue or organ damage, and the technical standards of stem cell application. The lack of ethics and management policies is also a problem that will need to be solved. Development of stem cell therapy in regenerative medicine may have the potential to revolutionize medicine, offering new ways to tackle many currently incurable and untreatable diseases, such as spinal cord injury, diabetes, Parkinson's disease, cardiovascular disease, and malignant or non-malignant hematological disorders. Although China has made remarkable achievements in basic research in the stem cell field over recent years, clinical and industrial applications of stem cells are not as advanced. Promoting the stem cell industry by introducing new policies and encouraging collaboration between research institutes, medical institutions, and pharmaceutical companies will be key to further developing the application of stem cells in the field of regenerative medicine.

(8) Metabolic heterogeneity and interactions in tumor microenvironments

Tumor cells are known to interact intensively with the surrounding stroma, known as the tumor microenvironment. The tumor microenvironment includes various cells, such as fibroblasts, immune cells, and endothelia cells, as well as many non-cellular components, such as the ECM, cytokines, and the complement system. The tumor microenvironment is characterized by hypoxia, low pH, and localized nutritional deficiency. The complex composition of the tumor microenvironment combined with the non-uniform tumor cell population result in metabolic heterogeneity, which fundamentally affects tumor development. The key scientific issues include reciprocal regulation between metabolic reprogramming and cellular signal transduction in tumors; metabolites functioning as signal molecules; crosstalk between tumor cells and the surrounding stroma cells, particularly immune cells; interplay between the metabolism of different organs and the local tumor microenvironment. During the development of research in this field, it has become clear that cancer metabolism is beyond normoxia glycolysis. Oxidative phosphorylation (OXPHOS) fueled by glucose, glutamine, and other nutrients/metabolites, and redox homeostasis of mitochondrion dramatically contribute to metabolic heterogeneity in tumor microenvironment. Mutations in oncogenes and tumor suppressors can lead to abnormal activation of signaling pathways that rewire the metabolic network in cells, highlighting the critical role of dietary intervention (or precision diet) based on the specific genetic background in cancer prevention and therapy. In addition, there has recently been increased interest in studying on metabolite sensing involved in signal transduction. With the exception of AMPK and mTOR, metabolites sensors remain largely unknown because of the huge number of different metabolites in the human body. Furthermore, there have been developments in targeted therapy of some pivotal enzymes such as IDH1/IDH2, which acquire novel enzymatic activity to produce oncometabolites when being mutated in tumors. Moreover, the metabolism and function of fibroblasts and immune cells in the tumor microenvironment are being widely investigated. Notably, increasing evidence is demonstrating the essential role of gut microbiota in tumor development and treatment. In China, there have been significant achievements in research into the effect of stressful conditions, such as hypoxia, bioenergy, and metabolite deficiency on tumor cell malignancies, while studies on metabolic heterogeneity of the tumor environment is also emerging. More recently, research on metabolites acting as signaling molecules and precision diets are becoming of central interest in this field.

(9) Precise diagnosis of diseases based on single-cell sequencing

Disease diagnosis based on single-cell sequencing involves sequencing the genome, transcriptome, or epigenome of single cell or a small number of cells. It is suitable for precise diagnosis in cases where a limited number of cells are available (such as germ cells, early embryos, and circulating tumor cells) or for tissues with high cell heterogeneity (such as the ovary, uterus, and tumor tissues). The key scientific issue in this field is how to improve the accuracy of disease diagnosis in order to achieve precise prevention and treatment of disease. Over recent years, the development of sequencing technology has greatly expedited research of genetic diseases, metabolic diseases, cancer, and other disorders, leading to major medical advances. At present, single-cell sequencing in global disease diagnosis mainly focuses on pre-implantation genetic testing, cancer typing, and follow-up medication guidance. The ongoing international project “Human Cell Atlas” is of great significance for the diagnosis of genetic and metabolic diseases; single-cell genome, transcriptome, and methylome sequencing can be used in cancer diagnosis to analyze tumor heterogeneity and achieve precision diagnosis to guide precise medical treatment. Moreover, it is possible to continuously track and monitor cancer development via these methods. In China, only ~40% of genetic diseases can currently be diagnosed and treated before embryo implantation, meaning that a high number of people still suffer from genetic diseases and cancers caused by genetic predispositions. However, the “Cancer Genome Atlas of China” has been gradually launched, and is dedicated to depicting the molecular map of cancer in order to provide effective guidance for cancer treatment in the Chinese population. A number of clinical studies based on single-cell sequencing technology are underway.

(10) Application and research of 3D printing technology in regenerative medicine

The application of 3D printing technology in regenerative medicine refers to the use of 3D printing technology to prepare tissues or organs matching the patient’s normal physiological structure and function, thus promoting tissue regeneration and functional reconstruction. 3D printing technology has been widely used to produce various medical models, rehabilitation medical devices, and personalized implants. However, for fabrication of tissues and organs with complete anatomical structure and physiological functions, there remain a number of key issues that need to be resolved. These primarily include successfully constructing 3D models with biological information, developing safe and stable bio-ink, developing 3D printing technology with sufficiently high resolution and efficiency, and providing nutrition to the tissue to maintain survival and functions competency after printing. 3D printing in the field of regenerative medicine has recently developed from single-cell printing to multi-cell printing, and is gradually moving toward tissue and organoid printing. Recent cutting-edge research has involved preparing new bio-printing inks using acellular matrix materials, and combining this with new novel high-speed and high-precision equipment to fabricate the vascular network, heart, lung, and other biological tissues and organs. In addition, 3D printing of some tissues, such as the cornea and skin, has already entered the clinical trial stage, highlighting the rapid progression of 3D printing technology. This trend of rapid development should be maintained in the future by the application of new innovative methods. In particular, we need to accelerate the development of bio-ink, bio-paper, and new types of bio-printing technology, materials, and equipment, as well as accelerate the pace of technical design and application of living bioreactors. With deep research and further development, 3D printing technology is expected to supply personalized regenerative medicine products with appropriate anatomical structures, mechanical properties, and biological functions. This will hopefully not only achieve the precise regeneration of tissues and organs, but also provide materials and theories for the continued development of regenerative medicine.

1.2 Interpretations for three key engineering research fronts

1.2.1 AI in biomedicine

AI is a technical science used to simulate and extend the theory, methods, techniques, and applications of human intelligence. The application of AI in biomedicine can increase accuracy and safety in a range of biomedical fields, such as health screening and warning, disease diagnosis and treatment, rehabilitation training and evaluation, medical services and management, drug screening and evaluation, and gene sequencing and characterization. These fields are all driven by medical data, including images, atlases, medical records, and other medical information sources, which can be processed by AI in various applications. For example, in health screening and warning, these applications include disease screening, chronic disease management, and wearable health monitoring devices. In disease diagnosis and treatment, AI can be applied to automatic lesion recognition, intelligent treatment decision-making, scientific evaluation of curative effects, robotic assisted surgery, and remote surgery. Rehabilitation training and evaluation applications include cognitive impairment rehabilitation, disability rehabilitation, robotic care, intelligent prostheses, and orthoses (including assistive exoskeleton devices). Applications in medical services and management include electronic medical record management, intelligent automatic drug delivery, and medical IoT services. Drug screening and evaluation applications of AI include drug target identification, drug screening, drug efficacy tests, drug safety evaluation, and adverse reaction data management. Finally, applications in the field of gene sequencing and characterization include gene screening, genome sequencing, gene editing, and individualized medical treatment. The application of AI in biomedicine is changing the approach of modern biomedical development. On the one hand, AI can benefit the whole medical process, including intelligent management of disease pathogenesis, precise diagnosis, safe treatment, and scientific evaluation. This has the result of significantly improving the professional efficiency of doctors, alleviating the shortage of doctors, improving the accuracy of diagnosis and treatment, and optimizing the allocation of high-quality medical resources. On the other hand, AI systems can enable real-time health monitoring and warning, and the rapid development of medical IoT, medical health hardware, and wearable health devices. Overall, the application of AI in biomedicine can aid innovation in medical technology and enable healthcare to progress to a new stage of quantitative analysis.

Some key scientific challenges for the application of AI in biomedicine are as follows: how to set up an effective framework to realize the standardized collection and safety-graded management of multi-source and multi-mode medical data; how to design new algorithms to perform unsupervised learning of small or limited datasets; how to integrate AI and traditional methods to perform safe and intelligent diagnosis and treatment; how to enhance the role of doctors in the process of AI interventions, and achieve effective cooperation of clinical human–computer intelligence; and how to formulate ethical management and legal supervision mechanisms for AI-related medical data in order to ensure the security of medical and personal information for patients and doctors. At present, hot topics for international research include: (1) Cancer and cancer diagnosis: Quantitative disease diagnosis and prognosis are organically combined by deep learning methods, leading to reductions in misdiagnosis rates and labor costs. This approach has been used in the pathological diagnosis of lung cancer, cervical cancer, breast cancer, gastrointestinal cancer, nasopharyngeal cancer, skin cancer, and other diseases. (2) Chronic disease management: Deep neural networks and fuzzy control methods can be applied for Alzheimer’s disease classification, hypertension management, and diabetes identification (diabetes classification and screening for diabetic retinopathy and other complications). This allows early warning and effective management of these chronic diseases. (3) Gene engineering: integrating the advantages of patient pathological sampling and genome sequencing. This method is conducted by gene screening, genome sequencing, and gene editing to achieve disease prediction and detection. Clinical guidelines and evidence-based medicine can then be combined to carry out personalized treatment. (4) Intelligent surgery: Intelligent robotics technology has been widely used in endoscopic surgery, orthopedics, neurosurgery, plastic surgery, and other fields. Two examples that have been widely used are the Da Vinci robot in the USA and the TianJi robot in China. The TianJi robot is the first orthopedic surgical robot created entirely in China, and received China Food and Drug Administration approval in 2016. It was produced by a team led by Professor Tian Wei from Beijing Jishuitan Hospital. This kind of AI technology has also been used in the automatic planning of surgical paths, autonomous decision-making of robot motion, and automatic evaluation of surgical effects. Meanwhile, the emergence of 5G technology may further promote the rapid development of telemedicine (particularly telesurgery). At present, China’s 5G-assisted robotic surgery is at the forefront of the international field. Professor Tian has achieved the milestone of being able to simultaneously control 2–3 robots remotely. Some researchers are also exploring the possibility of remotely controlling soft tissue robots such as Da Vinci; however, further research is needed to solve the delay between the image data and robot control. (5) Intelligent rehabilitation: virtual reality and intelligent robotics combined with AI technology can be applied to the rehabilitation of disabled people. Intelligent rehabilitation devices, such as artificial limbs, rehabilitation training robots, exoskeleton auxiliary devices and orthoses, escort robots, intelligent bed chairs, virtual reality rehabilitation systems, and electronic artificial larynxes, have been rapidly developed in recent years. (6) Drug R&D: AI technology has been widely used in drug target identification, drug screening, drug safety assessment, drug efficacy tests, and data collection. This has contributed to the pharmacological evaluation of traditional Chinese medicine, with the potential for a broad range of applications.

In recent years, AI has been subject to substantial market demand in the field of biomedicine, with an annual growth rate of 40%. The USA is the main consumer of biomedical AI technologies, followed by China and Europe. The overall development trends are as follows: The application of AI in biomedicine has developed from pathological diagnosis to clinical treatment; the integration of AI, robotics, 5G communication and other frontier technologies are changing the concepts and means of modern treatment; the application of AI in drug research and gene engineering is becoming a hot research topic; and the integration of AI and traditional Chinese medicine is attracting increasing attention.

The top 10 countries in terms of output of core research literature on the application of AI in biomedicine were all located in North America, Europe, and Asia. The USA, China, and the UK ranked as the top three countries, as shown in Table 1.2.1. The USA accounted for 52.24% of core papers, while China and the UK each accounted for over 10% of the core papers. The core literature from each country has been cited less than 70 times, indicating that this research field is in a stage of extremely active innovation, with rapidly changing methods of application. Moreover, the USA appears to be leading the global development of this research field. According to the collaborative network of the top 10 core paper-producing countries, there are close collaborative relationships among these countries, as shown in Figure 1.2.1.

Of the top 10 organizations producing core paper on application of AI in biomedicine, eight were in the USA and two were in Asia. The top three organizations were Harvard University, Stanford University, and Korea University. In terms of the number of published papers, the Chinese Academy of Sciences ranked sixth, as shown in Table 1.2.2. The results regarding collaborative networks between the top 10 core paper-producing organizations revealed collaborative relationships among many of these institutions, as shown in Figure 1.2.2.

Based on the statistical analyses described above, in the research front of “application of AI in biomedicine”, China now sits alongside other countries in terms of application, but is still catching up in terms of technological R&D. The current findings give rise to several suggestions for China: (1) Further expand the scope of application of AI technology in disease diagnosis, chronic disease prediction, and health monitoring, to benefit larger populations; (2) Continuously promote the application of AI technology in medical robotics, such as surgery, rehabilitation, and old-age care, to achieve safe, efficient, and efficient AI collaboration; (3) Strengthen the application of AI technology in medicine, especially in the field of traditional Chinese medicine (such as pharmacology and efficacy evaluation), to accelerate the process of innovative drug research, development, and testing; (4) Strengthen

Table 1.2.1 Countries or regions with the greatest output of core papers on “AI in biomedicine”

No.	Country/Region	Core papers	Percentage of core papers	Citations	Percentage of citations	Citations per paper
1	USA	350	52.24%	19 780	58.27%	56.51
2	China	100	14.93%	4 496	13.24%	44.96
3	UK	75	11.19%	3 966	11.68%	52.88
4	Germany	58	8.66%	3 181	9.37%	54.84
5	Italy	56	8.36%	2 215	6.53%	39.55
6	Canada	51	7.61%	3 004	8.85%	58.90
7	Netherlands	34	5.07%	2 271	6.69%	66.79
8	South Korea	34	5.07%	1 764	5.20%	51.88
9	Australia	32	4.78%	1 145	3.37%	35.78
10	Spain	31	4.63%	1 325	3.90%	42.74

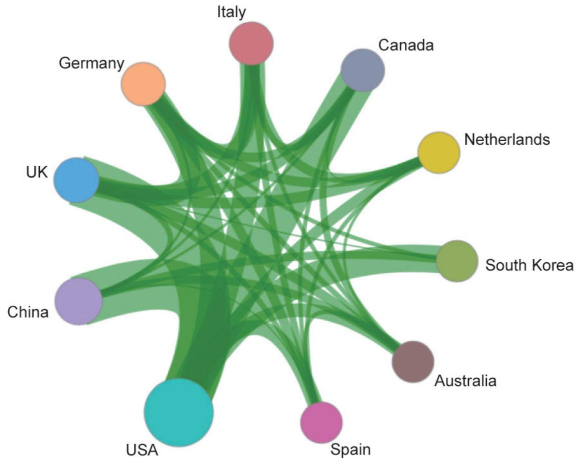

Figure 1.2.1 Collaboration network among major countries or regions in the engineering research front of “AI in biomedicine”

Table 1.2.2 Institutions with the greatest output of core papers on “AI in biomedicine”

No.	Institution	Core papers	Percentage of core papers	Citations	Percentage of citations	Citations per paper
1	Harvard Univ	59	8.81%	3714	10.94%	62.95
2	Stanford Univ	27	4.03%	2406	7.09%	89.11
3	Korea Univ	23	3.43%	1390	4.09%	60.43
4	Univ N Carolina	23	3.43%	1493	4.40%	64.91
5	Columbia Univ	17	2.54%	943	2.78%	55.47
6	Chinese Acad Sci	17	2.54%	793	2.34%	46.65
7	Johns Hopkins Univ	16	2.39%	665	1.96%	41.56
8	Univ Calif San Diego	15	2.24%	786	2.32%	52.40
9	Univ Washington	15	2.24%	742	2.19%	49.47
10	Univ Penn	114	2.09%	1117	3.29%	79.79

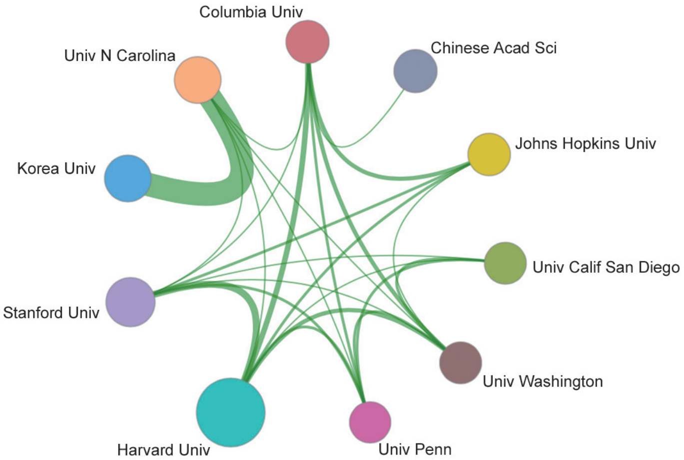

Figure 1.2.2 Collaboration network among major institutions in the engineering research front of "AI in biomedicine"

the cultivation of compound talents for medical science and engineering to avoid the separation of engineering development from clinical needs; and (5) Establish an international open innovation platform and collaboration mechanism to maximize the use of educational and scientific research resources.

1.2.2 Gut microbiota and immune homeostasis

The discovery of the important physiological function of human microbiota has subverted our understanding of human health and survival. In recent years, multiple studies have revealed the scale and complexity of microbial communities inhabiting the body surface and coelomic cavities of humans (over 10^{14} cells of bacteria, archaea, fungi, and viruses, dry weight approximately 1%–2% of total human body weight). These microbes colonize areas such as the gastrointestinal tract, oral cavity, skin, and urogenital tract. As these organisms contain 50–100 times more genes than human body, and encode a myriad of important biological processes, their genome is regarded as the "second genome" of the human body. These microorganisms and their living environment constitute human microbiota, which perform essential physiological functions over the course of human life. By directly or indirectly regulating the functions of the liver, digestive system, immune system, nervous system, and brain, they provide important maintenance of digestion, absorption, immune response, and material and energy metabolism, affecting human development, growth, health, and aging. This subverts the traditional concept of humans functioning as an independent species and opens a new concept of a mutually beneficial coexistence of human beings and microorganisms.

Nearly 80% of human microorganisms are located in the intestinal tract, forming the intestinal microbiota. Intestinal microbiota plays a significant role in disease by significantly affecting the processes of early warning, prevention, diagnosis, treatment, and rehabilitation. In recent years, multiple studies have identified key roles of intestinal microbiota in infections, liver diseases, metabolic diseases, autoimmune diseases, tumors, and brain and neuropsychiatric diseases. This has become a breakthrough for understanding the pathogenesis of major diseases. Research into important pathogenic microorganisms and alterations in intestinal microbiota before the occurrence of disease has opened a new chapter in disease prevention and early warning. New diagnostic methods based on intestinal microbiota alterations will not only become necessary tools for the diagnosis of unexplained and sudden infections, but will also be key for identifying and predicting the complex course of particular diseases, such as cirrhosis and hepatocellular carcinoma. Most chronic diseases are related to inflammation, and the intestine is one of the largest immune organs in the human body. The distribution of immune cells and the production of inflammatory factors can affect the occurrence and development of chronic diseases through direct or indirect contact with intestinal microorganisms and their metabolites. Metabolites of intestinal microorganisms have also been shown to affect the expression and regulation of intestinal inflammatory signals. Therefore, clarifying the interaction between the immune system, intestinal microorganisms, and microbial metabolism is of great significance for the prevention, intervention, and treatment of chronic diseases. The efficacy of most oral and injected drugs is closely related to the composition and function of intestinal microbiota. Relevant assessment of gut microbiota to prescribe accurate treatment could be highly significant for improving disease therapy and saving medical expenses. As well as its importance in directly or indirectly treating infections, liver diseases, metabolic diseases, autoimmune diseases, and tumors, gut microbiota regulation can overcome health problems that result from microbiota damage caused by the occurrence, development, and treatment of most diseases.

At present, the key scientific issues in R&D of the gut microbiota and immune homeostasis field are as follows: (1) How to integrate the theoretical and technical basis of modern medicine, biology, and information science to reveal the structure, function, and dynamicity of gut microbiota in humans, and to systematically analyze gut microbiota in immune development, maturity, and pathogenesis. (2) Elucidating the role and mechanism of gut microbiota in important pathological processes such as infections, liver diseases, metabolic diseases, and tumors. (3) Elucidating the role and mechanisms of gut microbiota in drug metabolism and the development of microbial resistance. The overall development trend is shifting from the study of immune regulation mechanisms of single gut microorganisms to the role and mechanism of gut microbiota in the establishment, maintenance, and regulation of host immune homeostasis and disease prevention. The research hotspots include: (1) The co-development and co-evolution of gut microbiota and the immune system; (2) The role and molecular mechanism of gut microbiota in regulating immune homeostasis and promoting host health; (3) The causal relationship and mechanism of gut microbiota imbalance on gut immune homeostasis and disease development; (4) The immune mechanisms and clinical applications of the effect of gut microbiota on disease therapies; (5) Disease early warning, diagnosis, and prognosis analysis based on alterations of gut microbiota and immune homeostasis; and (6) New drugs and therapeutic strategies for health promotion and disease prevention by regulating gut microbiota and immune homeostasis.

Publications relating to the front of "gut microbiota and immune homeostasis" are predominantly published by researchers in the USA, France, and China. China accounted for 14.29% of the published papers, and is one of the leading research countries in this front (Table 1.2.3). Figure 1.2.3 shows the collaborative relationships among these countries.

Of the ten major institutions with the greatest output of core papers in this front, the top four were in the USA and Belgium: Harvard University, The University of Michigan, the Catholic University of Louvain, and Emory University (Table 1.2.4). Figure 1.2.4 shows the collaborative relationships among these institutions.

Based on the above statistical analysis, China is currently in the same research situation as other countries in the "gut microbiota and immune homeostasis" research front, and the

Table 1.2.3 Countries or regions with the greatest output of core papers on "gut microbiota and immune homeostasis"

No.	Country/Region	Core papers	Percentage of core papers	Citations	Percentage of citations	Citations per paper
1	USA	34	53.97%	4062	53.80%	119.47
2	France	9	14.29%	1367	18.11%	151.89
3	China	9	14.29%	801	10.61%	89.00
4	Germany	5	7.94%	636	8.42%	127.20
5	Belgium	5	7.94%	807	10.69%	161.40
6	Canada	5	7.94%	407	5.39%	81.40
7	Japan	4	6.35%	556	7.36%	139.00
8	UK	4	6.35%	441	5.84%	110.25
9	Sweden	4	6.35%	549	7.27%	137.25
10	Switzerland	4	6.35%	457	6.05%	114.25

Figure 1.2.3 Collaboration network among major countries or regions in the engineering research front of “gut microbiota and immune homeostasis”

following suggestions apply for the future development of this field: (1) Integrate the existing multidisciplinary advantages: consolidate and develop the foundation of gut microbiota and immune homeostasis knowledge, and lay a good foundation for further development and research by promoting relevant research through industry–university–research linkage and international cooperation. (2) Fully exploit the advantages of China’s traditional medicine, investigating novel methods for gut microbiota and immune homeostasis R&D to avoid a lack of progress in this area. (3) Encourage cooperation among different disciplines regarding development strategy, and give full autonomy and initiative to all disciplines and teams. Develop the enthusiasm and initiative of researchers in a flexible and enterprising manner to allow movement into a new chapter of gut microbiota and immune homeostasis

Table 1.2.4 Institutions with the greatest output of core papers on “gut microbiota and immune homeostasis”

No.	Institution	Core papers	Percentage of core papers	Citations	Percentage of citations	Citations per paper
1	Harvard Univ	5	7.94%	732	9.70%	146.40
2	Univ Michigan	4	6.35%	587	7.77%	146.75
3	Catholic Univ Louvain	4	6.35%	706	9.35%	176.50
4	Emory Univ	4	6.35%	252	3.34%	63.00
5	RIKEN	3	4.76%	504	6.68%	168.00
6	INSERM	3	4.76%	550	7.28%	183.33
7	INRA	3	4.76%	216	2.86%	72.00
8	Washington Univ	2	3.17%	406	5.38%	203.00
9	Cent Queensland Univ	2	3.17%	322	4.26%	161.00
10	Monash Univ	2	3.17%	322	4.26%	161.00

RIKEN: Institute of Physical and Chemical Research; INSERM: Institut National de la Santé et de la Recherche Médicale; INRA: Institut National de la Recherche Agronomique.

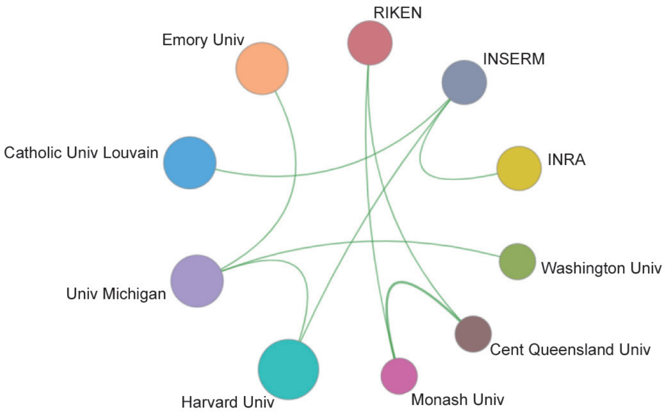

Figure 1.2.4 Collaboration network among major institutions in the engineering research front of “gut microbiota and immune homeostasis”

research in China. (4) Establish data standards for the gut microbiota and immune homeostasis field in China, including testing, analysis, and calculation. The government should organize and establish special agencies to coordinate and integrate the research resources of gut microbiota and immune homeostasis research in China, and build platforms for research cooperation and data collection to share at the national level. (5) Formulate relevant policies and designate enterprises to participate in all stages of research in the field of gut microbiota and immune homeostasis, and provide policy support to transform and promote the research results.

1.2.3 Neural computation and brain-inspired intelligence in the brain sciences

Neural computation and brain-inspired intelligence in the brain sciences is a multidisciplinary field incorporating neuroscience and mathematics. It is a new research field that involves theories and analytical methods of mathematics, computer science, neuroscience, biology, physics, cognitive psychology, social and behavioral science, and engineering. It also involves the analysis of big data, including genetics, neurons, neuroimaging, large-scale cognitive functions, and the environment, in multiple dimensions across time and space. In order to investigate mechanisms and dynamics of neural systems, decipher the principles of information processing/neural coding in the brain, and decode the mechanisms of brain function, the field incorporates methods such as quantitative analysis, computational models, and brain-inspired computation. The ultimate aim of the field is to use information technology to simulate higher functions of the brain and develop brain-inspired algorithms in order to establish new fields, such as novel models and algorithms of AI, brain-inspired chips, and brain-inspired engineering technology. In this way, this emerging field embodies the quote that ‘brain-inspired intelligence leads the development of artificial intelligence.’

Research of neural computation and brain-inspired intelligence in the brain sciences has two aspects: First, it involves neurobiological research into the essence of brain computation; second, it uses computational methods to decode the principles of brain intelligence, in order to create new technologies that cover several areas related to AI. Currently, AI, as represented by deep learning is rapidly changing methods of production and consumption. The products and models derived from it have been primarily applied to the Internet, software, digital business, cloud computing, healthcare, and industrial manufacturing. Taking industrial manufacturing as an example, the wave of digitalization is accelerating the development of industry globally. For example, Industry 4.0 in Germany employs algorithms and chips that enable the entire production process to independently perceive, learn, and make improvements, leading to a more flexible and individualized synthetic processes. According to a report published by Deloitte, the global market of AI may increase to 6 trillion USD by 2025. The next generation of AI, led by brain-inspired intelligence, provides very important and far-reaching opportunities. It has the potential to transform traditional industries, including healthcare, consumption, urban management, and industrial manufacturing, revolutionize their development, and potentially exert massive economic and social impact. Moreover, the field will also affect military security, information security, biological security, information analysis, and many other important areas.

Research of neural computation and brain-inspired intelligence in the brain sciences originated from research into AI; in particular, from areas fundamentally related to artificial neural networks and computational neuroscience. The pioneers in this field include the following: Von Neumann, the pioneer of the modern framework of computers, whose unfinished great work *The Computer and The Brain* focused on the relationship between the human neural system and the computer; Alan Turing, who used dynamic algorithms in physics to explain pattern formation in biological systems and proposed computing intelligence; Hodgkin and Huxley, who combined electrophysiological experiments and physical dynamics, and used differential equations to construct a precise model of single neural discharge; David Marr, who proposed the computational vision theory in 1940–1960; McCullc and Pitts, who proposed the neural model; Donald Hebb, who proposed the Hebb learning law; Rosenblatt, who proposed the concept of the perceptron algorithm; Shun’ichi Amari, who developed the mathematical basis of neural networks; and John Hopfield, who proposed a key energy function. Recently, researchers in brain sciences and mathematics, aided by the integration of computers and information technology, made two big breakthroughs in artificial neural network technology. On March 27, 2019, the creators of deep learning, Yoshua Bengio, Yann LeCun, and Geoffrey were awarded the Turing award of 2019. These three scientists created the basic concepts of deep learning. They presented impressive experimental results, and made great breakthroughs in the industry. The application of deep learning in various areas has been aided by achievements in computer vision, voice recognition, natural language processing, and robotics. However, the development of AI technology, in particular neural networks, over the past 30 years has been lacking in sufficiently deep integration of brain sciences and mathematics.

Neural computation in the brain sciences and brain-inspired intelligence involves multiple research fields surrounding the three main areas of neuroscience, brain sciences, and AI, including mathematics, computer science, information, (nano) microelectronics, cognitive sciences, psychology, neurosurgery, and basic medicine. One of the key scientific issues is investigating all of the intelligence-related mechanisms of brain information, cognition, consciousness, psychology, and memory, i.e., how to analyze neural circuit structures and neural information-processing mechanisms. It is clearly understood how neurons encode, transduce, and store neural information; however, it is not understood how the properties of these neurons are generated through local and long-range circuits, and that how neural circuit-based information produces various cognitive functions such as perception, emotion, thinking, decision-making, consciousness, and language. The other key scientific issue involves developing new theories, methods, and technologies to achieve human-like intelligence systems, including intelligent models, computing architectures, chip technologies, and related application technologies.

The front of neural computation in the brain sciences and brain-inspired intelligence include four aspects. The first is research based on the abnormal brain (brain disorders) to investigate various characteristics of the nervous system, including its structure and function, the mechanisms underlying its normal or abnormal state, and the computational strategies underlying its function. The second aspect is to develop non-destructive, non-invasive techniques and equipment with sufficient resolution (e.g. micrometers, nanometers, and milliseconds) for brain measurement. The third is to simulate and calculate the neuromorphic nature of trillions of synaptic interactions. The final aspect is to develop new intelligent computing architectures, integrating perception, cognition, psychology, consciousness, value, memory, decision-making, and learning and reasoning mechanisms.

In 2013, the USA launched the initiative Brain Research through Advancing Innovative Neurotechnologies (BRAIN), which is a collaboration of multiple institutes and agencies with a proposed total investment of approximately 3 billion USD. In addition to the National Institutes of Health (NIH) performing traditional brain disorder and medical research and developing new imaging and detection technologies incorporating large scientific devices, the Defense Advanced Research Projects Agency (DARPA) participated in order to investigate brain-inspired intelligence. In addition, the Intelligence Advanced Research Projects Agency (IARPA) currently funds the basic research project “Machine Intelligence from Cortical Networks (MICrONS).” The aim of MICrONS is to reversely engineer the brain’s algorithms and completely change machine learning, creating more powerful brain-inspired machine learning algorithms based on a deep understanding of brain representation, transformation, and learning rules. DARPA is committed to funding third-generation AI from 2018–2020 through both new and old projects aiming to break through the basic theory and core technology of AI by investigating machine learning and reasoning, natural language understanding, modeling and simulation, and human–machine fusion. On April 26, 2017, the US military launched Project Maven, a cross-functional team designed to carry out research on algorithm warfare-related concepts, technologies, and application. Project Maven aims to promote the military application of cutting-edge technologies such as AI, big data, and machine learning in order to maintain the US military’s technology and combat advantage. The EU also launched the Human Brain Project (HBP) in 2013, which focuses on simulating brain function.

Among the top 10 countries producing advanced core papers in the research front of “neural computation and brain-inspired intelligence in brain sciences,” the USA is clearly in the leading position, accounting for 47.33% of total publications. Germany and China rank second and third, respectively. However, China’s scientific research in this field is rapidly developing. The citation index of the core papers in this field ranged from 52.55 to 84.53 across the top 10 countries (Table 1.2.5), and the citation index of core papers produced in China was 66.05 This indicates that Chinese scholars in this field have the ability and potential to increase their impact with some improved efforts. According to the cooperation network of the top 10 core paper-producing countries, some close international collaborations have been developed, with the USA demonstrating collaboration with all other nine countries, demonstrating their strength and influence in this research field. The major countries cooperating with China include the USA, Germany, UK, Japan, Italy, and Switzerland (Figure 1.2.5).

Of the top 10 institutions in terms of core papers in this research front, the top three are from the USA and Germany, namely Stanford University, Harvard University, and the University of Tubingen. In terms of the number of published articles, the Chinese Academy of Sciences ranked fourth, as shown in Table 1.2.6. According to the collaboration network diagram of the top 10 core paper-producing institutions, some of the institutions have developed mutual collaborations (Figure 1.2.6).

Based on a statistical analysis of the above data, China is currently among the leading players with regard to research concerning neural computation in the brain sciences and brain-inspired intelligence. However, compared with developed countries, China still has some disadvantages which need addressing, such as relatively smaller research groups and limited international influence. In particular, the lack of cross-border multi-disciplinary research has restricted the progress of major science and technology key programs in this research field. Suggestions for the future development of this field in China are: first, to strengthen training and the introduction of multidisciplinary talents, and

Table1.2.5 Countries or regions with the greatest output of core papers on “neural computation and brain-inspired intelligence in the brain sciences”

No.	Country/Region	Core papers	Percentage of core papers	Citations	Percentage of citations	Citations per paper
1	USA	142	47.33%	10 394	49.09%	73.20
2	Germany	53	17.67%	2 936	13.87%	55.40
3	China	42	14.00%	2 774	13.10%	66.05
4	UK	34	11.33%	2 874	13.57%	84.53
5	Switzerland	26	8.67%	2 093	9.89%	80.50
6	Italy	24	8.00%	1 610	7.60%	67.08
7	France	22	7.33%	1 156	5.46%	52.55
8	Canada	20	6.67%	1 469	6.94%	73.45
9	South Korea	13	4.33%	965	4.56%	74.23
10	Japan	13	4.33%	797	3.76%	61.31

Figure 1.2.5 Collaboration network among major countries or regions in the engineering research front of “neural computation and brain-inspired intelligence in the brain sciences”

Table 1.2.6 Institutions with the greatest output of core papers on "neural computation and brain-inspired intelligence in the brain sciences"

No.	Institution	Core papers	Percentage of core papers	Citations	Percentage of citations	Citations per paper
1	Stanford Univ	18	6.00%	1627	7.68%	90.39
2	Harvard Univ	18	6.00%	1632	7.71%	90.67
3	Univ Tubingen	12	4.00%	534	2.52%	44.50
4	Chinese Acad Sci	10	3.33%	589	2.78%	58.90
5	Univ Oxford	9	3.00%	920	4.35%	102.22
6	Univ Zurich	9	3.00%	783	3.70%	87.00
7	Univ Toronto	9	3.00%	583	2.75%	64.78
8	Univ Coll London	8	2.67%	919	4.34%	114.88
9	Univ Calif San Diego	8	2.67%	681	3.22%	85.13
10	Korea Univ	8	2.67%	624	2.95%	78.00

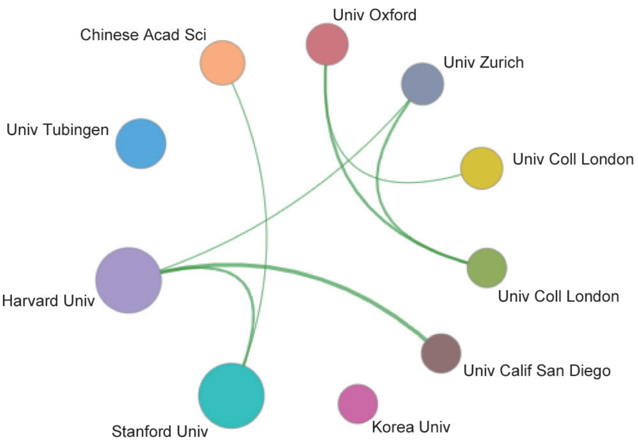

Figure 1.2.6 Collaboration network among major institutions in the engineering research front of "neural computation and brain-inspired intelligence in the brain sciences"

make use of the advantages of research funding, scientific facilities, and personnel remuneration. This will allow introduction and training of a number of interdisciplinary talents, including advanced experts in the fields of cognitive neuroscience, brain-inspired intelligence, and AI. The second suggestion is to further promote international scientific and technological collaborations between scientists in the fields of mathematics, physics, brain science, and computer science, as well as promote daily academic communications and in-depth dialogues. Third, China should accelerate the layout of scientific research and focus on the research of computational neuroscience and brain-inspired intelligence research in brain science. We need to integrate the key resources of the whole country, carry out collaborative innovation, focus on key scientific projects, and strive to gain opportunities to win on some key fundamental scientific issues. Fourth, by prediction and analysis of the likely future direction of the brain-inspired intelligence field, we should carry out research and discussions on ethics, data security, data sharing, and regulatory policy, and establish relevant regulations to protect the applications of brain-inspired intelligence technology.

2 Engineering development fronts

2.1 Trends in top 10 engineering development fronts

This section of the review describes the top 10 engineering development fronts in the field of medicine and health, which includes the fields of basic medicine, clinical medicine, pharmacy, medical informatics and biomedical engineering, public health, and preventive medicine, among other subjects. The three emerging fronts are "intelligence assisted diagnosis technology," "brain–computer interfaces," and "humanized animal models." Traditional research has focused on the engineering development fronts of "tumor immunotherapy technology," "genome editing," "disease prediction and intervention technology based on genomics big data," "intelligent wearable devices for health assistance," "stem cell-based tissue engineering and organ remodeling technology," "single cell analysis techniques," and "biomaterials for tissue regeneration and repair" (Table 2.1.1). All patents involved in these 10 fronts published between the years 2013–2018 are disclosed in Table 2.1.2.

(1) Tumor immunotherapy technology

Tumor immunotherapy (also known as cancer immunotherapy or immuno-oncology) is a method of applying immunological principles and methods to treat cancer by stimulating and enhancing the body's anti-tumor immune response. The main methods of tumor immunotherapy include cancer vaccines, specific monoclonal antibody targeted therapy, cytokine therapy, immune checkpoint blockade, and adoptive cell therapy. Tumor immunotherapy has developed rapidly in the field of translational clinical medicine over the past decade. Its application has improved the quality of life and significantly prolonged survival for a large number of cancer patients, giving new hope for curing various advanced cancers. It has played a significant role in promoting the development of contemporary medical technology, reforming the medical and health system, and developing social welfare and medical systems in various countries. The field of tumor immunotherapy originated from the first tumor vaccine in 1893. However, it was not until the 1990s that cytokine therapy, represented by interleukin-2 (IL-2), and monoclonal antibody targeted therapy brought dawn to the modern era of the field. In 2013, *Science* magazine ranked tumor immunotherapy at the top of the top 10 scientific breakthroughs. In the past 5 years, immune checkpoint inhibitor and chimeric antigen receptor T (CAR-T) cell immunotherapies have made major breakthroughs in various cancers and also promoted the development of other cancer immunotherapies. At present, tumor immunotherapy is the

Table 2.1.1 Top 10 engineering development fronts in medicine and health

No.	Engineering development front	Published patents	Citations	Citations per patent	Mean year
1	Tumor immunotherapy technology	5 145	16 846	3.27	2016.6
2	Intelligence assisted diagnosis technology	14 975	46 454	3.10	2016.2
3	Genome Editing	2 965	16 363	5.52	2016.7
4	Disease prediction and intervention technology based on genomics big data	11 529	36 476	3.16	2015.9
5	Brain–computer interfaces	5 060	13 702	2.71	2016.0
6	Intelligent wearable devices for health assistance	5 918	25 699	4.34	2016.4
7	Stem cell-based tissue engineering and organ remodeling technology	1 720	3 747	2.18	2015.7
8	Humanized animal models	757	1 900	2.51	2016.0
9	Single cell analysis techniques	2 500	6 669	2.67	2016.0
10	Biomaterials for tissue regeneration and repair	5 591	16 273	2.91	2015.7

Table 2.1.2 Annual number of core patents published for the top 10 engineering development fronts in medicine and health

No.	Engineering development front	2013	2014	2015	2016	2017	2018
1	Tumor immunotherapy technology	274	384	470	886	1379	1752
2	Intelligence assisted diagnosis technology	1237	1702	1930	2509	3164	4433
3	Genome editing	108	185	301	500	806	1065
4	Disease prediction and intervention technology based on genomics big data	1470	1547	1689	1943	2329	2551
5	Brain-computer interfaces	513	635	745	918	1120	1129
6	Intelligent wearable devices for health assistance	229	507	762	1241	1550	1629
7	Stem cell-based tissue engineering and organ remodeling technology	267	278	236	260	360	319
8	Humanized animal models	89	112	98	123	145	190
9	Single cell analysis techniques	289	321	329	388	525	648
10	Biomaterials for tissue regeneration and repair	852	913	748	925	1062	1091

fourth type of cancer treatment that has been proven to have significant clinical efficacy after the traditional three treatment types: surgery, radiotherapy, and chemotherapy.

(2) Intelligence assisted diagnosis technology

Intelligence assisted diagnosis refers to computers providing assisted disease analysis in clinical diagnosis to help doctors make better use of information and improve the quality and efficiency of diagnosis and treatment. The application of intelligence assisted diagnosis technology can not only alleviate the current shortage of medical resources, but also effectively promote the reform of the medical system, and help to gradually form a new business strategy in the medical field. Intelligence assisted diagnosis technology originated in the late 1950s, and has since developed in three stages. The first stage mainly involved knowledge engineering through the sorting, construction, and accumulation of medical knowledge. The second development stage involves shallow semantic learning and reasoning, which integrates traditional machine learning and feature engineering. The third stage is autonomous learning of medical diagnosis decision reasoning, which is characterized by massive medical data and deep learning methods. At present, intelligence assisted diagnosis technology is in rapid development between the second and third stages.

The key technical problems that need to be solved for the next stage of development of intelligence assisted diagnosis technology are: 1) The representation learning of medical knowledge; 2) The construction of complex reasoning models based on diagnosis and treatment ideas; 3) The generalization of intelligent assisted diagnosis results; and 4) The biological interpretability of intelligent diagnosis models. In recent years, global investment in the field of medical AI has shown a trend of rapid rise. The domestic intelligence assisted diagnosis related industry has also risen rapidly. In 2017, the industry output value in China reached more than 13 billion CNY, with an annual increase of 40.7%. It is predicted that the output value may exceed 20 billion CNY in 2018 according to the current development trend. At present, many technology giants are stepping up their efforts in the field of intelligence assisted diagnosis technology. For example, international companies such as IBM, Google, and Siemens have been engaged in the field of intelligence assisted diagnosis for many years, and have accumulated a large number of invention patents and formed certain technical barriers. Domestic high-tech enterprises such as Tencent, United Imaging Healthcare, and iFLYTEK have also made important breakthroughs over recent years, and are gradually adapting the development path of intelligence assisted diagnostic technology to China's national conditions.

(3) Genome editing

Genome editing refers to the deletion, insertion, replacement, or single base substitution of DNA in the genome by deploying nuclease and cellular DNA repair machinery. This technique is currently in broad use to construct animal models, screen for new therapeutic targets, and improve agronomic traits of livestock and crops. Furthermore, it has made the transition from the bench to clinical trials, for example in the development of anti-virus drugs, CAR-T cell therapy, and blood disease treatments. From the emergence of first generation meganuclease in 1994 to the more recent popularization of zinc finger nucleases (ZFN) and transcriptional activation-like effector nucleases (TALEN), gene editing has continuously been evolving in terms of its precision and efficacy. In 2012, the repurposing of the bacterial anti-phage CRISPR/Cas system for RNA-guided DNA-targeting brought a qualitative leap in the endeavors to re-write genetic information in any organism. It is now possible to achieve simple and efficient editing at single or multiple loci in living cells. In addition, multiple derivative technologies empowered by CRISPR/Cas, such as gene activation, gene silencing, RNA editing, epigenetic engineering, and base editing, provide a powerful tool repertoire for biomedical research to uncover the pathogenesis, mechanism, and treatment of disease. In the coming years, the predicted technical challenges for the development of gene editing technologies include: 1) Improvement of gene editing efficiency and precision; 2) Robust delivery systems for gene editing reagents; 3) Expansion of editable sequence space; 4) More accurate off-target evaluation methods; and 5) Development of RNA editing tools. Since the debut of CRISPR/Cas in 2012, this field has been explored enthusiastically, as evidenced by the explosion in relevant research publications inspired by the enormous potential for the application of CRISPR/Cas, particularly in the clinical sciences.

(4) Disease prediction and intervention technology based on genomics big data

Genomics big data are multi-layer, high dimensional data represented by the human genome, transcriptome, epigenome, and metabolome. In recent years, the rapid development of second- and third-generation DNA sequencing technologies have resulted in rapid growth of genomics data, and have also brought new opportunities and challenges for disease research. On the one hand, genomics data can aid our understanding of the causes underlying complex diseases, thus promoting their prevention and treatment. On the other hand, the complexity of genomics data means that its transformation into practical clinical application can be very slow. In terms of disease prediction, compared with traditional biophysical and biochemical tests, genomics data-based methods have the advantages of being early, accurate, and non-disruptive. For example, the detection of cfDNA in blood can help doctors to screen for early stage cancers. During disease intervention, genomics data can increase the accuracy of drug usage and treatment. Analyses of genomics data for different patients can also facilitate the implementation of personalized medicine. However, three issues need to be resolved before genomics data can be applied to clinics on a larger scale. First, our understanding of genomics big data is not yet deep enough, therefore key genes associated with the onset of specific diseases and their mechanisms of action need to be further tested and confirmed. Second, sequencing technologies need to be further developed, and there are only very few chips that can currently be used for disease detection. Third, the laws and regulations relevant for the clinical application of genomics big data need to be improved. In particular, issues such as the deposition and retrieval of genomics data urgently need to be resolved. For example, although disease-related epigenetics changes have been reported in several thousand research articles, only four FDA-approved drugs are available for their treatment. As a large country with a huge population, China has a big advantage in genomics big data research, and has carried out many such studies on Chinese populations. However, several bottlenecks still exist. For example, China relies heavily on the USA for sequencing technologies, machines, and reagents. In addition, The National Genomics Data Center, which is designed for data management and sharing, was only established very recently. In the future, with the development of sequencing technology and advancement of research, genomics big data will play an increasingly important role in disease prediction and intervention.

(5) Brain–computer interfaces (BCIs)

Brain–computer interfaces (BCIs) measure central nervous system (CNS) activity and convert it into an artificial output that replaces, restores, enhances, supplements, or improves natural CNS outputs, thereby changing the ongoing interactions between the CNS and its external or internal environment. BCI technology collects signals of CNS activity through sensors placed either on the scalp or in the cranium. After signal processing, feature extraction, and pattern recognition, it is possible to obtain the control intentions of the CNS, cognitive or psychological states, and states of nervous diseases. In this way, BCIs can provide new control and communication channels or rehabilitation methods for disabled patients with movement and language disorders. It can also provide more information output channels for healthy people. With the development of electroencephalography (EEG) signal acquisition and processing technology, BCI technology has gradually entered clinical application. It has performed well in clinical rehabilitation of patients with brain injury or other neurological diseases such as stroke and attention deficit disorder. BCI technology can also provide motor function solutions for patients with motor dysfunction disorders such as high paraplegia and amyotrophic lateral sclerosis (ALS). It can also provide objective indicators for the detection and identification of emotion, fatigue, and state of consciousness. Due to its broad prospects in the military and civilian fields, China, the USA, and several countries in Europe attach great importance to the investment in BCI technology research. In recent years, a series of technological start-up companies have emerged, and technological breakthroughs and new products have been launched. Clinical rehabilitation and daily application products based on BCI technology have reached a substantial market level, which is continuing to grow rapidly. The key factors to promote BCI technology breakthroughs in the future will be high spatial resolution of electrical and magnetic brain signal acquisition technology, intelligent signal processing technology, and high-integration software and hardware platforms. The deep integration of BCI technology with materials science, nanotechnology, robotics, and AI will bring new hope for the diagnosis and rehabilitation of many nervous diseases. In time, this may also allow development of BCI technology into a generally available high-performance information interaction channel between brain and computer, bringing great benefits in the military and civilian fields in the future.

(6) Intelligent wearable devices for health assistance

Intelligent wearable devices for health assistance can sense, record, analyze, regulate, and even treat diseases and maintain health. With the development of electronics and information technology, the intelligent wearable health assistance device has gone through three development stages: version 1.0, based on smart phone applications; version 2.0, based on independent communication and intelligent operation; and the new version 3.0, based on edge computing and personal data services. With the improvement of public health awareness and the further development of edge computing, cloud computing, big data, and AI technologies, intelligent wearable health assistance devices have entered a rapid growth period. They are able to provide intelligent operations to monitor, prevent, and treat diseases without temporal or geographical limitations. These characteristics allow both long-term and emergency treatments for the elderly, or those suffering from occupational, chronic, or high-risk diseases. It is predicted that by 2020 the number of wearable devices will increase by 15.3% from the previous year to reach a total of 198.5 million, and the global market size will reach 6 billion USD. With the development of electronic computing hardware and software algorithm performance, together with the improvement of modern medical disease databases and the strong support of national policies, intelligent wearable health assistance devices have a promising future. Specific improvements are that the product features of wearable devices are more focused, the personal database is more abundant, the user experience is better, and remote medical treatment is more popular. These devices will improve the popularity, coverage, and professionalism of medical care while significantly reducing the cost, making significant contributions towards the goals of disease prevention and promotion of public health.

(7) Stem cell-based tissue engineering and organ remodeling technology

Stem cell-based tissue engineering and organ remodeling technology is a biomedical engineering technology that produces bionic tissues and organs by integrating stem cells with biomaterials, tissue microenvironment elements, 3D bio-printing, and other tissue engineering construction technologies. Key technical problems in this field include: producing stem cells with the biological functions of target tissues and organs or stem cell-derived functional cells; producing biodegradable materials with suitable biomechanics and good biocompatibility; providing suitable blood supply, nutrients, cellular matrix, and other tissue microenvironment elements; and developing advanced 3D bio-printing and other construction technologies. The development of this technology will promote in-depth exploration of developmental processes, functional maintenance of normal tissues and organs, disease development, and the regeneration and functional reconstruction of tissues and organs; realize reconstructions of tissues and organs by mimicking their composition, structure, and function, realizing the transformation from basic research to clinical application in humans; provide new technologies, methods, and products for human health; provide a feasible way to improve length and quality of patients' life; and provide strong support for the development of emerging industries of tissue engineering and regenerative medicine.

(8) Humanized animal models

Humanized animal models are experimental animals with stable chimerism, leading to expansion and differentiation of human cells, tissues, or organs. Such animal models are appropriate for modeling development and metabolism of human organs of interest, as well as disease progression, giving the opportunity for fundamental R&D of therapeutic strategies. Generally, key factors to allow further development of the humanized animal model field include the methods for human cell transplantation and chimerism, development of appropriate recipient animals, system standardization, and large-scale application. Indispensably, the humanized animal model can provide a multi-dimensional and multi-model *in vivo* microenvironment for the progression of important human diseases, aiding the development of new drugs and therapeutic strategies. In contrast to other animal models, humanized animal models can be used to overcome the obstacle of species specificity, which has largely limited studies of some important human species-dependent pathogens. Currently, the humanized animal model field and relevant technologies are highly valued and are rapidly being developed both in China and internationally. Humanized animals with chimerism of single primary human tissues or organs have been widely applied in studies of some important pathogens. Important future research directions for this field include humanized animals derived from stem cells and even somatic cells, and humanized animals with chimerism of multiple homologous tissues or organs, in particular for immune system research. This next generation of humanized models will largely promote research on infectious diseases, malignant tumors, and autoimmune diseases. Another important consideration is to establish the standardization and large-scale application of humanized animal models.

China has established a good foundation in this field, having developed a variety of humanized animal models based on target needs and superior resources, highlighting its strong sustainable development capabilities.

(9) Single cell analysis techniques

Single cell analysis is the study of genomics, transcriptomics, proteomics, and metabolomics at the single cell level. It is by far the most powerful approach to investigate the physiological states, developmental trajectories, regulatory circuitry, and interactions of cells in heterogeneous populations. Since the first study of a single cell transcriptome in 2009, there has been tremendous growth in the fields of next-generation sequencing (NGS), mass cytometry (CyTOF), and single molecule imaging technologies. This has made it possible to simultaneously perform multiomic single cell analyses of the transcriptome, genome, metabolome, or proteome of up to one million cells per study. Since 2016, the international project “Human Cell Atlas” consortium have begun to use cutting-edge single cell analyses to create reference profiles of all cell types of the human body. The newly constructed atlases of the immune system, nervous system, and epithelia have already proven instrumental in identifying and annotating specialized or diseased cells in normal and pathological conditions. At the same time, single cell analyses of tumors, embryos, and patients undergoing therapy have provided unprecedented insights into the dynamic process of cellular differentiation and the evolution of intra-patient heterogeneity. With further improvement of single cell technologies, along with the continued decrease in associated experimental costs, the next decade will likely see the application of single cell analysis in constructing the cell atlas of all major human diseases, building the foundation for rapid and accurate diagnosis of abnormal cells at all stages of pathogenesis. This will undoubtedly facilitate our ability to fully realize the potential of precise and personalized medicine.

(10) Biomaterials for tissue regeneration and repair

Biomaterials for tissue regeneration and repair refers to materials that can play an important role in regeneration and functional repair of tissues and organs either through the physical and chemical properties of the materials, or through the loading of cells, growth factors, or drugs, for example. At present, the design and fabrication strategies of the biomaterials for tissue regeneration and repair field include restoring the shape and structure of the defective area, simulating the physiological microenvironment of tissue growth and development, precisely regulating the process of tissue regeneration, and realizing the interaction between host and material. The interdisciplinary nature of biomaterials for tissue regeneration spans the fields of materials science, biology, medicine, and advanced manufacturing technology. So far, biomaterials for tissue regeneration and repair have been successfully applied to repair defects in tissues such as the skin, blood vessels, cornea, bone, cartilage, and soft and hard oral tissues. Moreover, combined with digital medical technology and 3D printing technology, biomaterials for tissue regeneration and repair can also be used for personalized and precise treatment of biological defects. In addition to the applications in tissue regeneration, biomaterial-constructed microtissues, organoids, or organ chips are useful in developmental and pharmacology research, for example drug screening. Due at least partly to the increase in the aging population, the number of patients with injuries of human tissues and organs is increasing. Repairing tissue and organ defects using only traditional treatments is difficult, which has led to an increase in the need for biomaterials for tissue regeneration and repair. It is estimated that the global market for regenerative medicine will grow from 10.07 billion USD in 2018 to 48.97 billion USD in 2025, with a compound annual growth rate of 25.4%. As an important part of the regenerative medicine industry, the biomaterials for tissue regeneration and repair field has great potential for further development. Currently, there are several obstacles in the R&D of biomaterials for tissue regeneration and repair, such as inadequate induction leading to slow tissue regeneration, limitations in the regeneration of large tissues and organs due to the complexity of their structure and function, and differences in body status. Therefore, the development trends of this field include enhancing the inductive activity of biomaterials, constructing functional regenerative materials for large complex tissues and organs, and comprehensively realizing the needs for individualized regeneration.

2.2 Interpretations for three key engineering development fronts

2.2.1 Tumor immunotherapy technology

Tumor immunotherapy (also known as cancer immunotherapy or immuno-oncology) is a method of applying immunological principles and methods to treat cancer by stimulating and enhancing the body's anti-tumor immune response. The main methods of tumor immunotherapy include cancer vaccines, specific monoclonal antibody targeted therapy, cytokine therapy, immune checkpoint blockade, and adoptive cell therapy. Tumor immunotherapy has developed rapidly in the field of translational clinical medicine over the past decade. Its application has improved the quality of life and significantly prolonged survival for a large number of cancer patients, giving new hope for curing various advanced cancers. It has played significant roles in promoting the development of contemporary medical technology, reforming the medical and health system, and developing social welfare and medical systems in various countries. The field of tumor immunotherapy originated from the first tumor vaccine in 1893, but it was not until the 1990s that cytokine therapy, represented by IL-2, and monoclonal antibody targeted therapy brought dawn to the modern era of the field. In 2013, *Science* magazine ranked tumor immunotherapy at the top of the Top 10 scientific breakthroughs. In the past 5 years, immune checkpoint inhibitor and CAR-T cell immunotherapies have made major breakthroughs in various cancers and also promoted the development of other cancer immunotherapies. At present, tumor immunotherapy is the fourth type of cancer treatment that has been proven to have significant clinical efficacy after the three traditional treatment types: surgery, radiotherapy, and chemotherapy.

Presently, the development of tumor immunotherapy technology depends on solving the following key technical problems: (1) Discovery of tumor-specific targets; (2) Investigation of tumor immune escape mechanisms and development of appropriate countermeasures; (3) investigation of methods to overcome solid tumor microenvironments and heterogeneity; (4) Identification and application of tumor biomarkers; (5) Development of more durable and effective immunotherapy; (6) Improvement of the safety of immunotherapy; and (7) Development of new tumor immunotherapy and combination therapy techniques.

The number of cancer patients is currently increasing year by year, and the market demand for cancer therapy is huge. As a new industry that revolutionizes the standards and concepts of cancer treatment, the global market of tumor immunotherapy is growing rapidly. In 2016, the global market for tumor immunotherapy reached 61.9 billion US dollars, and with the increasing market demand it is expected to grow to 120 billion USD by 2021, with a compound annual growth rate above 14%. With the rapid development of the field, the number of tumor immunotherapy drugs and the number of R&D institutions and enterprises involved in tumor immunotherapy projects will continue to increase globally. The level of R&D of Chinese scientific research institutions in the tumor immunotherapy field is gradually integrating with this global expansion. Of the patents for new tumor immunotherapy technologies in 2013–2018, Chinese applications accounted for 18.51%, second only to the USA, indicating that China is one of the most prolific countries in the field of tumor immunotherapy. However, the total number of patents cited and the average number of citations from Chinese research are still considerably lower than those from the USA, and the quality of Chinese patents requires further improvement.

The current fronts in the field of international tumor immunotherapy research include: (1) Cancer vaccines: an active immunotherapy method that induces a patient's own specific immune response by use of an active substance containing a tumor-specific or tumor-associated antigen to overcome the immunosuppressive state and inhibit tumor growth. (2) Specific monoclonal antibody targeted therapy: monoclonal antibodies designed against tumor-specific antigens which lead specifically to tumor cell death either directly, by modifying tumor cell signaling cascades or tumor–matrix interactions, or indirectly, through antibody-dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). (3) Cytokine therapy: cytokines with multiple biological activities can either exert direct anti-tumor effects or indirectly enhance an anti-tumor immune response. For example, tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) directly affect tumor cell growth and survival, whereas IL-2 and interferon alpha (IFN-α) promote the growth and activation of T cells and natural killer (NK) cells. (4) Immune checkpoint blockade: a method of blocking immunosuppressive signals with specific antibodies of immunological checkpoint molecules (such as PD-1/PD-L1, CTLA-4), which activates immune cell recognition and permanently kills tumor cells. (5) Adoptive cell therapy: a method involves isolation of immunocompetent cells from tumor patients, followed by *in vitro* expansion and functional identification. The cells are then returned to the patient, killing tumor cells directly or stimulating the body's immune system to kill tumor cells. The current representative adoptive cell therapy, CAR-T, involves the use of genetic engineering technology to modify T cells to specifically identify tumor cells in a non-MHC-restricted manner. The modified T cells then directly and efficiently kill the tumor cells in a precise, targeted manner, which has been shown to have long-lasting effects in cancer treatment.

The global incidence of cancer has continued to rise over recent years. China has the largest number of cancer patients of all countries globally, and the incidence and mortality of cancer are still constantly rising. According to *Global Oncology Trend 2019*, the market for cancer treatment in China was 9 billion USD in 2018, and has been growing at an annual rate of 11.1%. The development of tumor immunotherapy improves the length and quality of life for many cancer patients, and even allows many to return to work, greatly reducing social burden and promoting economic development. With the advancement of China's innovative drug policy and the strengthening of R&D in the cancer immunotherapy field in recent years, an increasing number of scientific research institutions and pharmaceutical companies have entered the market, especially in the emerging field of adoptive cell therapy. At present, the overall level of China's tumor immunotherapy development is in a good position to make great strides forward. In the future, based on the promising results achieved in the field, by giving full play to the advantages of clinical sample resources in China, optimizing resource allocation, and encouraging cooperation and exchange among industries, universities, and research institutes, China will closely integrate with the frontier disciplines such as genomics, proteomics, and systems biology, and keep in pace with the cutting-edge of applied immunology research. In this way, it should be possible for China to overcome technical blockades, establish a leading position in the global field of immunotherapy, and ultimately make important contributions to the development of medical treatments and human health.

More than 4000 patents have been applied for in the area of tumor immunotherapy technology within the past five years. The USA, China, and Germany are ranked as the top three countries in terms of the number of active patents. The patents applied by Chinese researchers account for 18.51% of the global total, second only to the USA, indicating that China is one of the most prolific countries in the field of tumor immunotherapy. However, the average citation frequency of Chinese patents is 1.72, compared to 4.28 in the USA (Table 2.2.1), suggesting that China needs to make improvements in patent quality. As shown in the collaboration network of the top 10 patent-producing countries (Figure 2.2.1), the USA, Switzerland, UK, and China have close collaborations in the field of tumor immunotherapy technology.

The top three institutions in terms of patent output in the field of tumor immunotherapy technology are The Board of Regents of the University of Texas System, Dana-Farber Cancer Institute Inc., and Bristol-Myers Squibb Company (Table 2.2.2). In addition, the collaboration network of the top 10 patent-producing institutions shows cooperation between Novartis AG and The Trustees of the University of Pennsylvania, as well

Table 2.2.1 Countries or regions with the greatest output of core patents on "tumor immunotherapy technology"

No.	Country/Region	Published patents	Percentage of published patents	Citations	Percentage of citation	Citations per patent
1	USA	2786	55.50%	11 927	71.27%	4.28
2	China	929	18.51%	1 596	9.54%	1.72
3	Germany	266	5.30%	1 321	7.89%	4.97
4	UK	198	3.94%	554	3.31%	2.80
5	Switzerland	189	3.76%	1 829	10.93%	9.68
6	Japan	178	3.55%	234	1.40%	1.31
7	France	163	3.25%	765	4.57%	4.69
8	Canada	81	1.61%	230	1.37%	2.84
9	Israel	78	1.55%	159	0.95%	2.04
10	Australia	71	1.41%	50	0.30%	0.70

as between F. Hoffmann-LA Roche AG and Genentech Inc. (Figure 2.2.2) is close.

Between 2013 and 2018, the proportion of patents for “specific monoclonal antibody targeted therapy” and “adoptive cell therapy” was relatively large, and continues to increase year by year. Chinese patents accounted for 15.76% of the global total in the “specific monoclonal antibody targeted therapy” field, whereas USA patents accounted for 60.39%. Chinese patents also accounted for 34.54% of the global total in the field of “adoptive cell therapy”, while USA patents accounted for 44.13%. In 2018, Chinese patents accounted for 36.50% of the global total in the “adoptive cell therapy” field, compared to 43.10% for USA patents (Figure 2.2.3), indicating that China is increasing its focus on emerging areas of adoptive cell therapy. The overall tendency appears to be that China is catching up with the USA in terms of the number of patents.

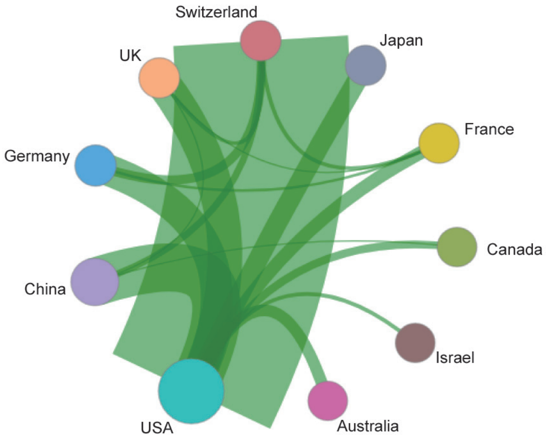

Figure 2.2.1 Collaboration network among major countries or regions in the engineering development front of “tumor immunotherapy technology”

Based on the above statistical analysis, China is currently at a similar level as other leading countries in terms of the number of patents in the engineering development front of “tumor immunotherapy technology”, indicating that China is one of the leading countries in the field of tumor immunotherapy.

2.2.2 Intelligence assisted diagnosis technology

Intelligence assisted diagnosis refers to computers providing assisted disease analysis in clinical diagnosis to help doctors make better use of information and improve the quality and efficiency of diagnosis and treatment. The application of intelligence assisted diagnosis technology can not only alleviate the current shortage of medical resources, but also effectively promote the reform of the medical system, and help to gradually form a new business strategy in the medical field. Intelligence assisted diagnosis technology originated in the late 1950s, and has developed in three stages. The first stage mainly involved knowledge engineering, through the sorting, construction, and accumulation of medical knowledge. The second development stage involves shallow semantic learning and reasoning, which integrates traditional

Table 2.2.2 Institutions with the greatest output of core patents on “tumor immunotherapy technology”

No.	Institution	Published patents	Percentage of published patents	Citations	Percentage of citation	Citations per patent
1	TEXA	113	2.25%	405	2.42%	3.58
2	DAND	100	1.99%	725	4.33%	7.25
3	BRIM	89	1.77%	896	5.35%	10.07
4	USSH	88	1.75%	287	1.71%	3.26
5	NOVS	87	1.73%	1280	7.65%	14.71
6	UPEN	83	1.65%	1324	7.91%	15.95
7	HOFF	77	1.53%	689	4.12%	8.95
8	IMMA	67	1.33%	215	1.28%	3.21
9	GETH	65	1.29%	570	3.41%	8.77
10	SLOK	59	1.18%	367	2.19%	6.22

TEXA: The Board of Regents of the University of Texas System; DAND: Dana-Farber Cancer Institute Inc.; BRIM: Bristol-Myers Squibb Company; USSH: The United States of America as represented by the Secretary department of Health & Human Service; NOVS: Novartis AG; UPEN: The Trustees of the University of Pennsylvania; HOFF: F.Hoffmann-LA Roche AG; IMMA: Immatics Biotechnologies GmbH; GETH: Genentech Inc.; SLOK: Memorial Sloan Kettering Cancer Center.

machine learning and feature engineering. The third stage is autonomous learning of medical diagnosis decision reasoning, which is characterized by massive medical data and deep learning methods. At present, intelligence assisted diagnosis technology is in rapid development between the second and third stages.

The key technical problems that need to be solved for the next stage of development of intelligence assisted diagnosis technology are: (1) The representation learning of medical knowledge; (2) The construction of complex reasoning models based on diagnosis and treatment ideas; (3) The generalization of intelligence assisted diagnosis results; and (4) The biological interpretability of intelligent diagnosis models. In recent years, the global investment in the field of medical AI has shown a trend of rapid rise. The domestic intelligence assisted diagnosis related industry has also risen rapidly. In 2017, the industry output value in China reached more than 13 billion CNY, with an annual increase of 40.7%. It is predicted that he output value may exceed 20 billion CNY in 2018 according to the current development trend. At present, many technology giants are stepping up their efforts in the field of intelligence assisted diagnosis technology. For example, international companies such as IBM, Google, and Siemens have been engaged in the field of intelligence assisted diagnosis for many years, and have accumulated a large number of invention patents and formed certain technical barriers. Domestic high-tech enterprises such as Tencent, United Imaging Healthcare, and iFLYTEK have also made important breakthroughs over recent years, and are gradually adapting the development path of intelligence assisted diagnostic technology to China's national conditions.

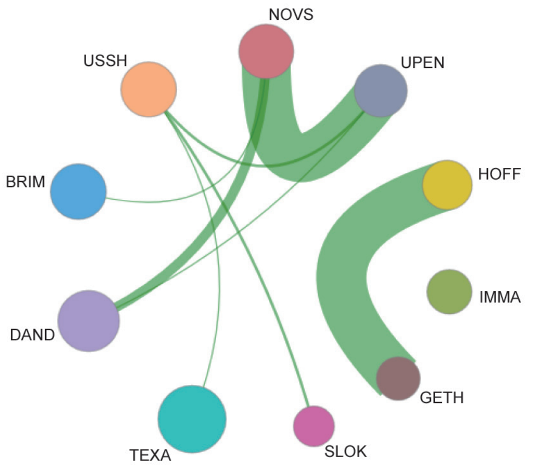

Figure 2.2.2 Collaboration network among major institutions in the engineering development front of "tumor immunotherapy technology"

China contributed one of the highest numbers of patent applications in the front of "intelligence assisted diagnosis technology" of all countries during the period 2013 to 2018, with its proportion of the global total reaching 25.1%. However, the quality of China's patents needs to be further

Figure 2.2.3 Major countries or regions producing patents in hot fields of "tumor immunotherapy technology"

improved. Moreover, the total number of patents and average number of patent citations are still far below those of the USA and other developed countries.

The current frontiers in the field of intelligence assisted diagnosis technology research include: (1) The mathematical model of deep learning for medical big data is the basis of intelligence assisted diagnosis technology. Medical data describing molecules, cells, tissues, and organs usually has a multidimensional attribute. The mathematical model of deep learning can be used as an interface that connects the multidimensional data, and illustrates the logical relationships of the data. (2) Radiomics that takes advantage of AI technology to comprehensively process images produced by X-ray, CT scan, magnetic resonance imaging, positron emission tomography, ultrasound, and pathology provides doctors with stacked intelligence assisted decision-making, effectively improving their efficiency and diagnostic accuracy. (3) AI-based gene diagnosis uses intelligent analysis methods to identify cancer cell biomarkers from massive genetic data and develop AI-assisted decision systems to track and predict the activities of cancer cells in the body. (4) Integration of physical sign monitoring and intelligent analysis to integrate intelligent analysis methods into the continuous and real-time monitoring by wearable devices. A deep learning network model can be constructed and applied to electrocardiogram data analysis and continuous blood glucose monitoring, thus to give early warning for potential diseases and provide significant references for subsequent diagnoses. (5) Clinical data intelligence assisted decision-making uses AI to develop a more structured clinical data management platform and allow modeling of clinical data. It can monitor clinical signs, assess diagnostic methods, and visualize the predicted result, thus embedding clinical decision planning in the process of clinical treatment, guiding doctor's medical judgment. (6) Intelligence assisted natural language processing mainly involves researching AI-based processing and application of natural language to provide personalized medical services to patients. It can improve the efficiency of medical treatment and the quality of medical records. (7) Medical AI specialized chips guarantee sufficient computing power for the application of intelligence assisted diagnosis. They not only allow adaption to the real-time requirements of professional medical scenarios, but are also required to fully support the speed and optimization of various deep learning algorithms which are used in medical diagnosis. (8) Medical assistance robots are an interdisciplinary field, incorporating not only intelligence assisted diagnosis technology, but also robotics, biological materials, and other advanced technologies. Through the organic combination of these techniques, it is possible to promote the development of capsule robots, surgical robots, and other high-end medical equipment.

With the rapid development of AI, there has been a steady increase in the accumulation of AI technology in the medical scene. As a typical technology in this field, intelligence assisted diagnosis has attracted extensive attention from the international community. In China in particular, the unique advantage of the high availability of medical big data provides the required foundations for the development of intelligence assisted diagnosis technology. However, due to mismatches in information systems between hospitals, the “isolated information island” phenomenon has become apparent. Meanwhile, a serious lack of standardization and structure has led to a reduction in the amount of useable medical data. These problems seriously restrict the development of intelligence assisted diagnosis technology. Although it is claimed that the currently developed intelligence assisted diagnostic systems have high diagnostic accuracy, they are still far from practical application. The development of intelligent diagnostic models by enterprises, universities, and research institutes has always been based on self-provided limited databases, whereas practical application scenarios are often more complex. Therefore, large-scale clinical testing is required to assess whether new intelligent diagnostic models have any practical value. However, the increasingly close cooperation between industry and hospitals will establish a multi-center open platform for clinical verification of intelligence assisted diagnosis, creating favorable conditions for its clinical application. On the other hand, intelligence assisted diagnosis technology brings many obstacles to the identification of medical liability, particularly in the determination of the scope of responsibility for medical negligence. It is therefore necessary to improve the laws and regulations regarding intelligence assisted diagnosis, and clarify the subjects of medical liability and the scope of rights and responsibilities. China has gathered a large number of high-end talents in the field of medical AI through the establishment of a state-level open platform. This platform accelerates the development of intelligence assisted diagnosis technology to a deeper interdisciplinary direction, and aims to meet future technical challenges.

In the past five years, more than 1400 patents on intelligence assisted diagnosis technology have been applied for. The USA, China, and Japan are ranked as the top three countries in terms of the greatest numbers of active patents. Although Chinese patents account for 25.01% of the global total (Table 2.2.3), the average cited frequency of China (0.93, Table 2.2.3) is much lower than that of the USA and other developed countries. This suggests that China needs to improve the quality of its patents. As shown in the collaboration network of the top 10 patent-producing countries (Figure 2.2.4), the USA and Germany are in close collaboration with each other.

The top three institutions in terms of the number of active patents in this field are Volcano, IBM, and Siemens (Table 2.2.4). In addition, the collaboration network of the top 10 patent-producing institutions shows collaboration exists between Siemens AG and Cerner Innovation Inc. (Figure 2.2.5).

2.2.3 Genome editing

Genome editing refers to the deletion, insertion, replacement, or single base substitution of DNA in the genome by deploying nuclease and cellular DNA repair machinery. This technique is currently in broad use to construct animal models,

Table 2.2.3 Countries or regions with the greatest output of core patents on “intelligence assisted diagnosis technology”

No.	Country/Region	Published patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	USA	6556	43.78%	33 029	71.10%	5.04
2	China	3745	25.01%	3 485	7.50%	0.93
3	Japan	967	6.46%	2 047	4.41%	2.12
4	South Korea	868	5.80%	1 073	2.31%	1.24
5	Germany	541	3.61%	1 500	3.23%	2.77
6	Netherlands	488	3.26%	1 041	2.24%	2.13
7	Canada	297	1.98%	1 244	2.68%	4.19
8	Israel	209	1.40%	920	1.98%	4.40
9	Taiwan of China	193	1.29%	318	0.68%	1.65
10	France	190	1.27%	330	0.71%	1.74

Table 2.2.4 Institutions with the greatest output of core patents on “intelligence assisted diagnosis technology”

No.	Institution	Published patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	PHIG	465	3.11%	1101	2.37%	2.37
2	IBMC	352	2.35%	478	1.03%	1.36
3	SIEI	318	2.12%	1257	2.71%	3.95
4	SMSU	204	1.36%	582	1.25%	2.85
5	HEAR	198	1.32%	793	1.71%	4.01
6	GENE	130	0.87%	327	0.70%	2.52
7	BSCI	112	0.75%	319	0.69%	2.85
8	MEDT	95	0.63%	519	1.12%	5.46
9	UBIO	88	0.59%	343	0.74%	3.90
10	CRNR	79	0.53%	213	0.46%	2.70

PHIG: Volcano Corporation; IBMC: International Business Machines Corporation; SIEI: Siemens AG; SMSU: Samsung Electronics Co., Ltd.; HEAR: HeartFlow Inc.; GENE: General Electric Company; BSCI: Boston Scientific Scimed Inc.; MEDT: Medtronic MiniMed Inc.; UBIO: uBiome Inc.; CRNR: Cerner Innovation Inc.

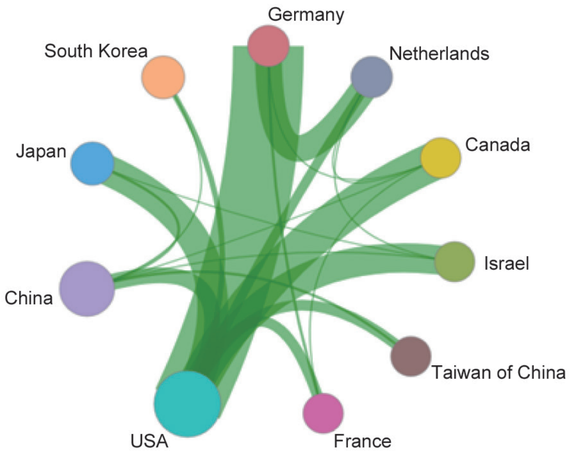

Figure 2.2.4 Collaboration network among major countries or regions in the engineering development front of "intelligence assisted diagnosis technology"

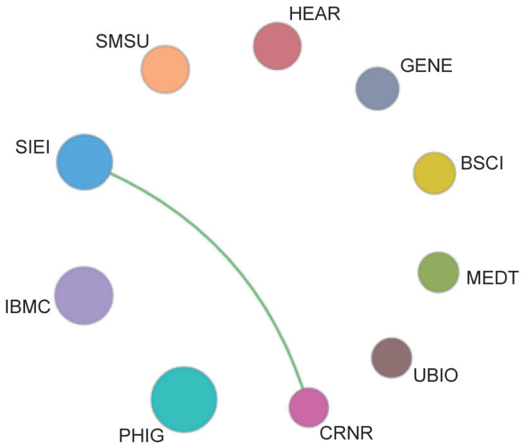

Figure 2.2.5 Collaboration network among major institutions in the engineering development front of "intelligence assisted diagnosis technology"

screen for new therapeutic targets, and improve agronomic traits of livestock and crops. Furthermore, it has made the transition from the bench to clinical trials, for example in the development of anti-virus drugs, CAR-T cell therapy, and blood disease treatments. From the emergence of first generation meganuclease in 1994 to the more recent popularization of ZFN and TALEN, gene editing has continuously been evolving in terms of its precision and efficacy. In 2012, the repurposing of the bacteria anti-phage CRISPR/Cas system for RNA-guided DNA-targeting brought a qualitative leap in the endeavors to re-write genetic information in any organism. It is now possible to achieve simple and efficient editing at single or multiple loci in living cells. In addition, multiple derivative technologies empowered by CRISPR/Cas, such as gene activation, gene silencing, RNA editing, epigenetic engineering, and base editing, provide a powerful tool repertoire for biomedical research to uncover the pathogenesis, mechanisms, and treatment of disease.

In the coming years, the predicted technical challenges for the development of gene editing technologies include: (1) Improvement of gene editing efficiency and precision; (2) Robust delivery systems for gene editing reagents; (3) Expansion of editable sequence space; (4) More accurate off-target evaluation methods; and (5) Development of RNA editing tools. Since the debut of CRISPR/Cas in 2012, this field has been explored enthusiastically, as evidenced by the explosion in relevant research publications inspired by the enormous potential for the application of CRISPR/Cas, particularly in the clinical sciences. Correspondingly, a large number of relevant patent applications have been filed. The top 3 countries or regions in terms of the number of gene editing-related patents are the USA, China, and Spain. Chinese patents make up 28.23% of the global total, second only to the USA, demonstrating China as one of the leading-edge countries in strategic engineering deployment (Table 2.2.5). As shown in the cooperation network of the top 10 patent-producing countries (Figure 2.2.6), the USA has a close relationship with Switzerland. It is worth noting that the core technical gene editing patents, especially those at relatively early stages, are held by European countries and the USA. This results in China having a relatively low average citation frequency of 2.14, ranking 7 in the top 10 countries. The top three institutions in terms of the number of active patents are Harvard College, Massachusetts Institute of Technology, and The Broad Institute Inc. (Table 2.2.6). In addition, the collaboration network among the top 10 institutions shows a close relationship among these top 3 institutions (Figure 2.2.7).

The current hot topics of gene editing include: (1) Treatment of disease caused by point-mutations by base editing: Gene editing enables us to modify target DNA defects on a molecular level, thereby curing diseases that are caused by DNA mutation. Encapsulating the gene editing system in virus allows specific targeting to the pathogenic site, allowing local *in vivo* gene therapy to cure diseases such as inherited blindness or hearing loss. For diseases bearing,

Table 2.2.5 Countries or regions with the greatest output of core patents on "genome editing"

No.	Country/Region	Published patents	Percentage of published patents	Citations	Percentage of citations	Citation per patent
1	USA	1433	48.33%	12 651	77.31%	8.83
2	China	837	28.23%	1789	10.93%	2.14
3	Spain	142	4.79%	28	0.17%	0.20
4	Switzerland	90	3.04%	651	3.98%	7.23
5	France	80	2.70%	669	4.09%	8.36
6	South Korea	79	2.66%	145	0.89%	1.84
7	Japan	68	2.29%	139	0.85%	2.04
8	Germany	55	1.85%	203	1.24%	3.69
9	UK	49	1.65%	203	1.24%	4.14
10	Canada	38	1.28%	120	0.73%	3.16

Table 2.2.6 Institutions with the greatest output of core patents on "genome editing"

No.	Institution	Published patents	Percentage of published patents	Citations	Percentage of citations	Citation per patent
1	HARD	144	4.86%	2696	16.48%	18.72
2	MASI	133	4.49%	4066	24.85%	30.57
3	BROD	97	3.27%	3619	22.12%	37.31
4	REGC	79	2.66%	510	3.12%	6.46
5	SAGM	47	1.59%	672	4.11%	14.30
6	EDIT	44	1.48%	521	3.18%	11.84
7	GEHO	42	1.42%	531	3.25%	12.64
8	CECT	33	1.11%	542	3.31%	16.42
9	CRIS	33	1.11%	131	0.80%	3.97
10	STRD	31	1.05%	121	0.74%	3.90

HARD: Harvard College; MASI: Massachusetts Institute of Technology; BROD: The Broad Institute Inc.; REGC: The Regents of the University of California; SAGM: Sangamo Therapeutics Inc.; EDIT: Editas Medicine Inc.; GEHO: The General Hospital Corporation; CECT: Cellectis; CRIS: CRISPR Therapeutics AG; STRD: The Board of Trustees of the Leland Stanford Junior University.

non-local phenotype, such as thalassemia, *ex vivo* editing of an individual patient's cells, followed by transfusion of the successfully edited cells back to the patient, would achieve a similar effect. (2) Genetically engineered immune cell therapy for cancer treatment: In CAR-T cell therapy, personalized cancer therapy is achieved by gene editing of an individual patient's killer T cells to prepare them against the patient's specific cancer cells, followed by transfusion of these customized killer T cells back to the patient. (3) Epigenetic or transcriptomic editing treatment for epigenetically inherited and degenerative diseases: These therapies utilize CRISPR/Cas9 to turn epigenetic markers on or off *in vivo*. For example, activating the gene that stimulate glia cells to neurons could be the key to curing neurodegenerative diseases. (4) Development of more sensitive clinical diagnostic kits: To detect trace amounts of pathogenic nucleic acid sequences in samples, it is crucial to amplify the correct signal. The correct signal can be identified by Cas, which locks onto the target nucleic acid sequence, and the signal can then be amplified with the help of a signal cascade amplification system. (5) High-throughput screening technologies for new therapeutic target identification: The CRISPR/Cas9 system can be applied to high-throughput screening, allowing the identification of new drugs. (6) Construction of animal models: Efficient construction of animal models using miniature model organisms such as drosophila, eelworm, rat, and mouse, and

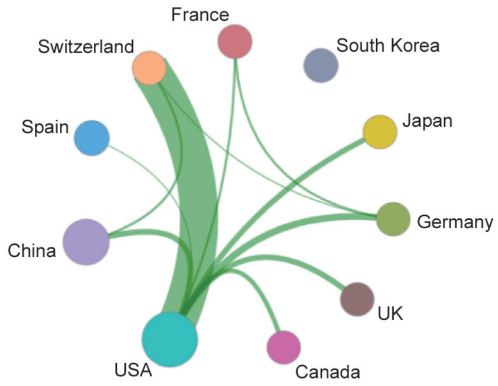

Figure 2.2.6 Collaboration network among major countries or regions in the engineering development front of "genome editing"

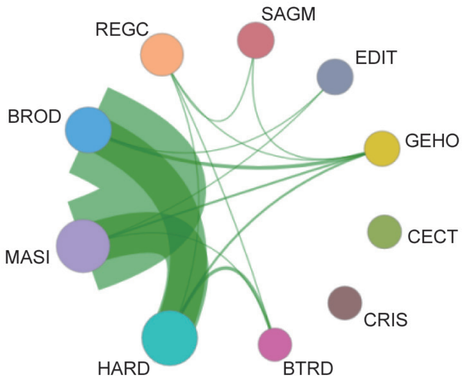

Figure 2.2.7 Collaboration network among major institutions in the engineering development front of "genome editing"

large organisms such as non-human primates, has reached an unprecedented precision, providing robust tools for both science research and clinical trials. (7) Breeding of animals and plants for agronomic trait improvement: This involves gene editing of animals and plants to obtain high quality breeds with the desired traits for agriculture and animal husbandry.

The huge potential of this technique will undoubtedly boost social evolution, particularly within the healthcare sector. As aging of the global population accelerates and patient ratios continue to rise, there will be a huge demand for gene therapy. Gene-based drugs are likely to represent the blue ocean market highly desired by countries all over the world. However, China is not necessarily an easy winner in this competing market; although it is tightly following the trend in patent applications, there is strong core competitiveness in European countries and the USA. China's aim is to discover new drugs, which requires practicing fundamental technology, and this comes with extremely high patent fees. Moreover, while the gene therapy industry has decades of history in western countries, in China the field is still immature. Despite its research quality approaching that of European countries, Chinese inchoate industrial structure displays a lack of referential experience or supporting social policies. Furthermore, the off-target effects of the gene editing technique hinder its progress, even in industry. Accurate off-target detection and further development of high precision editing tools are common goals of scientists in this field globally.

Participants of the Field Group

Leaders

CHEN Saijuan, ZHANG Boli

Academicians

GU Xiaosong, HUANG Luqi, LI Song, LI Zhaoshen, SUN Yinghao, TIAN Zhigang, XU Jianguo, ZHANG Zhiyuan, DONG Jiahong

Other Experts

ZHOU Rongbin, GUO Deyin, YI Fan, LIU Bing, YANG Hui, ZHOU Dawang, CHENG Gong, LIAO Zhuan, ZOU Wenbin, WANG Yueying, SHI Jian, XIAO Jianru, JIANG Jianxin, WANG Linhui, XIAO Liang, JIN Gang, SHENG Yuan, LI Hanzhong, ZHENG Jiasheng, WANG Haifeng, XU Qin, BAI Guo, LU Jinxing, QIN Chengfeng, QIN Chuan, ZHANG Jianzhong, ZHOU Dongsheng, CHENG Xunjia, SONG Hongbing, XIA Ningshao, LI Zhenjun, ZHAO Dongmei, CHENG Tong, ZHONG Wu, ZHOU Xinbo, FENG Jiannan, OUYANG Shaolian, HAN Qianqian, JIANG Qin, GU Zhongze, YAO Dezhong, ZHENG Hairong, LI Luming, XU Lai, XIAO Xiaohe, GUO Lanping, GAO Yue, YANG Hongjun, ZHANG Weidong, DUAN Jin'ao, XIAO Wei, LI Haiyan, LI Jiansheng, WANG Yongjun, MAO Jingyuan, WANG Baohe, WANG Hongwu, HUANG Yuhong, FAN Guanwei, ZHANG Han, YANG Jing

Secretary Group

ZHANG Wentao, ZHAO Xilu, XI Xiaodong, YAN Xiaoyu, CHEN Yinyin, DAI Yuting, QIAO Niu

Data Support Group

QIU Xiaochun, DENG Peiwen, WU Hui, FAN Rong, KOU Jiande, LIU Jie, TAO Lei, JIANG Hongbo, CHEN Daming, LU Jiao, MAO Kaiyun, FAN Yuelei, YUAN Yinchi

Report Writers

Engineering Research Front

TIAN Wei, HAN Xiaoguang, LI Lanjuan, FENG Jianfeng, XIE Xiaohua, XU Li, ZHAO Yuanjin, ZHOU Caicun, XIA Ningshao, CHENG Lin, LEI Qunying, QIAO Jie, DAI Kerong

Engineering Development Front

FAN Xiaohu, ZHENG Hairong, YANG Hui, BAO Yiming, MING Dong, TIAN Xiaohua, GU Xiaosong, XIA Ningshao, LIU Feng, JIANG Xinquan