VIII. Medicine and Health

1 Engineering research fronts

1.1 Trends in top 10 engineering research fronts

The top 10 engineering research fronts in the fields of medicine and health include public health and preventive medicine, basic medicine, clinical medicine, medical informatics and biomedical engineering, and traditional Chinese medicine (TCM) (Table 1.1.1). These 10 fronts also include "improving public health and epidemic prevention systems and emergency mechanisms," "global research on COVID-19 and emerging highly pathogenic viruses," "gut microbiota imbalances and diseases," "stem cell therapies and clinical translation," "medical robots and intelligent medicine," "brain-inspired intelligence research," "construction of the human single-cell atlas," "the collection and use of real-world evidence to support drug research and clinical application," "new target discovery and translation of active compounds in TCM," and "pathogenesis, precision diagnosis, and treatment strategy of hereditary tumors in the Chinese population."

The publication dataset of the top two fronts contains data from January 2014 to August 2020 as they are closely related to the COVID-19 epidemic. The publication dataset of the remaining seven fronts contains data from January 2014 to December 2019. All core papers detailing with these topics are listed in Table 1.1.2.

(1) Improving public health and epidemic prevention systems and emergency mechanisms

Public health and epidemic prevention systems and emergency mechanisms primarily refer to the institutions, personnel, and management operating mechanisms for the prevention and control of traditional and emerging infectious diseases, and also to the mechanisms in place to allow for a joint response in the event of a public health emergency by facilitating the deployment of medical and health resources. A modern, scientific, and complete public health and epidemic prevention system is important for any countries, and the establishment of such a system is an essential practice in the modern governance system and in the evaluation of governance capabilities. With the global outbreak of COVID-19, the need to improve the research

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	Improving public health and epidemic prevention systems and emergency mechanisms	240	2 558	10.66	2017.2
2	Global research on COVID-19 and emerging highly pathogenic viruses	2 707	195 743	72.31	2016.8
3	Gut microbiota imbalances and diseases	197	29 028	147.35	2015.9
4	Stem cell therapies and clinical translation	531	46 376	87.34	2015.3
5	Medical robots and intelligent medicine	3 272	218 591	66.81	2015.7
6	Brain-inspired intelligence research	509	43 834	86.12	2015.7
7	Construction of the human single-cell atlas	118	17 262	146.29	2016.4
8	The collection and use of real-world evidence to support drug research and clinical application	105	3 828	36.46	2016.6
9	New target discovery and translation of active compounds in traditional Chinese medicine	91	3 986	43.80	2015.6
10	Pathogenesis, precision diagnosis, and treatment strategy of hereditary tumors in the Chinese population	594	6 893	11.60	2016.6

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	2019	2020
1	Improving public health and epidemic prevention systems and emergency mechanisms	21	18	48	49	41	23	40
2	Global research on COVID-19 and emerging highly pathogenic viruses	486	408	454	387	311	95	566
3	Gut microbiota imbalances and diseases	32	47	57	41	19	1	–
4	Stem cell therapies and clinical translation	195	115	113	80	24	4	–
5	Medical robots and intelligent medicine	882	827	596	526	342	99	–
6	Brain-inspired intelligence research	130	119	101	95	55	9	–
7	Construction of the human single-cell atlas	11	21	30	27	22	7	–
8	The collection and use of real-world evidence to support drug research and clinical application	7	14	32	25	20	7	–
9	New target discovery and translation of active compounds in traditional Chinese medicine	22	24	20	15	10	0	–
10	Pathogenesis, precision diagnosis, and treatment strategy of hereditary tumors in the Chinese population	99	91	95	107	83	119	–

of public health and epidemic prevention systems and emergency response mechanisms has increased dramatically, and effective research ideas have become increasingly clear. Infectious diseases are still the main issues threatening human health, which disturb the order of production and life, thereby bringing harm to society and economy. Therefore, international community must recognize the importance of the prevention and control of infectious diseases, thereby to protect the health and safety of individuals and promote economic construction and social harmony. Additionally, public health security has become an important part of national security, and the status of disease prevention and control system as the core component of the public health system has been further clarified. Disease prevention and control services are part of the public health service functions provided by the government and require strong guarantees from public finances and institutional mechanisms.

(2) Global research on COVID-19 and emerging highly pathogenic viruses

The COVID-19 outbreak has triggered a global crisis, and the pandemic threat posed by other potentially highly pathogenic viruses should not be overlooked. Through the collaboration of the scientists in the whole world, major progress has been made in the basic knowledge and application research of the severe acute respiratory sydrome coronavirus 2 (SARS-CoV-2), which has profoundly deepened our understanding of the virus and the diseases due to it. Particularly, Chinese scientists have identified SARS-CoV-2 as the pathogen in a short time, and shared the full genome sequence with the world. The structures of this novel coronavirus and its key coding proteins have been resolved rapidly. Reliable cell and animal models were established for further research and development of vaccines and pharmaceuticals. Several vaccines and therapeutic drugs are undergoing the phase III clinical trial. The domestic contagion was effectively controlled in a short time. All of these achievements have embodied the strength of Chinese science and technology. The critical scientific issues of the global research on novel coronavirus and emerging highly pathogenic viruses include the origin, evolution and the molecular mechanism of interspecies transmission to and among humans of the novel coronavirus, the mechanisms of the viral life cycle and severe viral infection. The global research on novel coronavirus and emerging highly pathogenic viruses focus on the structures and functions and their mechanisms of the genome and encoding proteins of novel coronavirus, clinical progress and outcome, the mechanism of infection and immune protection, the screening and evolution of new vaccines and anti-virus pharmaceuticals. Generally, in the future, the research will rely

on a more integrated application of single-cell sequencing, system biology, reverse genetics, big data, and artificial intelligence (AI) for the further investigation of the infection, pathogenesis, and transmission of novel viruses. More next-generation vaccines and drugs based on rational design will come to clinical trials in the near future.

(3) Gut microbiota imbalances and diseases

The gut microbiota is essentially an "important organ," as it plays an indispensable role in human health and disease. The human gastrointestinal tract contains trillions of bacteria, fungi, and viruses. Among them, there are more than 1000 species of bacteria alone, and this is equivalent to approximately 10-fold the number of human cells. The number of genes encoded by these bacteria is 50–100 times that of the human host, and these encoded genes are equivalent to the "second genome" of humans and contain important genetic information. Gut microbes and their living environment constitute the gut microbiota, and this microbiota is an important maintainer of host digestion and absorption, immune response, and material and energy metabolism. The gut microbiota constantly undergoes alterations with age, and these changes are closely related to aging and longevity. Research examining gut microbiota imbalances and diseases has enhanced the traditional understanding of major diseases such as infection, liver disease, tumors, and metabolic diseases in medicine, and the findings from these research projects have facilitated revolutionary changes in the prevention, diagnosis, and treatment of various diseases. Research examining gut microbiota and diseases has attracted a great deal of attention from governments, scientific and technological circles, enterprises, and the public. Developed countries regard it as an important field in their national science and technology strategic planning.

(4) Stem cell therapies and clinical translation

Stem-cell therapies are therapies that involve the use of stem cells or their derived substances. Stem cells are unspecialized cells that possess the abilities of self-renewal and differentiation into any cell within an organism. These cells exist in embryos, fetal/perinatal tissues, and adult tissues. Based on this, stem cells are classified into the following: embryonic stem cells, perinatal stem cells, and adult stem cells. Stem cells are also named according to their function, such as hematopoietic stem cells (HSCs), neural stem cells, and mesenchymal stromal/stem cells (MSCs). The development of different gene manipulation technologies has allowed researchers to produce novel stem cells such as induced pluripotent stem cells (iPSCs) and gene-edited stem cells. Typically, stem cells exert their therapeutic activities through either cell replacement and/or paracrine regulation. Therapies using stem-cell–derived substances such as exosomes are considered as cell-free stem cell therapies. Thus, stem cell therapies include stem cell replacement therapy and stem-cell-based tissue function and structure improvement therapy.

The key issues related to the clinical translation of stem cells include the best choice of stem cells for a given clinical indication; the large-scale, cost-effective, and reproducible production of high-quality stem cells or their derivatives; the analysis of the mechanism and biological effects of stem cells; the development of gene-edited stem cells; stem-cells-based gene therapy and combination therapy of stem cells; and large-sample and multicenter clinical trials and follow up of their long-term effects.

HSCs transplantation is the typical stem cell replacement therapy that has been used for over half a century and that plays an important role in the treatment of several blood diseases, autoimmune diseases, and genetic diseases. In recent decades, HSCs, due to their ability to differentiate into vascular endothelial cells, have been used to effectively treat critical limb ischemia and other vascular diseases. Therapies using autologous stem cells, iPSC-derived tissue stem cells, Human Leukocyte Antigen type-matched allogenic HSCs, and gene-edited HSCs are all cell replacement therapies. MSCs possess high immunomodulatory and pro-angiogenic activities in addition to multipotent differentiation ability, and therefore MSCs have been used in the treatment of a variety of diseases, including tissue regeneration, autoimmune diseases, vascular diseases, and inflammatory diseases. Heterotopic transplantation of autologous MSCs can be considered as a replacement therapy. In contrast, allogenic MSCs obtained from several different tissues have also been reported to be effective in the treatment of a variety of diseases and do not exhibit clearly visible immune rejection. The combination of the replacement therapy and the functional improvement of different stem cells can result in a synergetic effect. For example, co-transplantation of HSCs and MSCs has been shown to promote the engraftment of HSCs and to decrease the development of graft-versus-host disease.

(5) Medical robots and intelligent medicine

AI is a technical science, which can be used to simulate and extend the theory, methods, and applications of human intelligence. Intelligent medicine is the science of assisting or replacing humans in the field of medical behavior through AI technology. The application of AI in biomedicine can increase the accuracy and safety within a number of biomedical fields, including health screening and early warning, disease diagnosis and treatment, rehabilitation training and evaluation, medical services and management, drug screening and evaluation, and gene sequencing and characterization. Medical robots are an important branch of intelligent medicine.

The research status of medical robots and intelligent medicine can be summarized primarily according to six aspects. 1) Health screening and warning primarily involves disease screening, chronic disease management, and wearable health monitoring devices. Alzheimer's disease classification, hypertension management, diabetes identification (diabetes classification and screening for diabetic retinopathy and other complications) can be performed using deep neural networks and fuzzy control methods to achieve early warning and effective management of chronic diseases. 2) Disease diagnosis and treatment primarily involves automatic lesion recognition, intelligent treatment decision-making, scientific evaluation of curative effects, robotic-assisted surgery, and remote surgery. Quantitative disease diagnosis and prognosis are organically combined by in-depth learning methods. 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, and it can reduce the misdiagnosis rate and labor cost. 3) Rehabilitation training and evaluation primarily involves cognitive impairment rehabilitation, disability and rehabilitation, robotic care, intelligent prosthesis, and orthosis (including assistive exoskeleton devices). Virtual reality and intelligent robotics combined with AI technology can be applied to the rehabilitation of disabled people. Intelligent rehabilitation devices have been rapidly developed in recent years, and these devices include artificial limbs, rehabilitation training robots, exoskeleton auxiliary devices and orthoses, escort robots, intelligent bed chairs, virtual reality rehabilitation systems, and electronic artificial larynx. Medical robots are also used extensively in clinics. 4) Medical services and management primarily involve electronic medical record management, intelligent automatic drug delivery, and the medical Internet of Things services. 5) Drug screening and evaluation primarily involves drug target identification, drug screening, drug efficacy tests, drug safety evaluation, and adverse reaction data management. AI technology has been widely used in drug target identification, drug screening, drug safety assessment, drug efficacy tests, and data collection, and this technology has also been used in the pharmacological evaluation of TCM and possesses potential for many broad applications. 6) Gene sequencing and characterization primarily involves gene screening, genome sequencing, gene editing, and individualized precise medical treatment. This technology integrates the features of patient pathological sampling with extracted genome sequencing data, and involves using gene screening, genome sequencing, and gene editing to achieve disease prediction and detection. Clinical guidelines and evidence-based medicine can be combined to achieve personalized treatment.

The overall developmental trends include the advancement of the application of AI in biomedicine from pathological diagnosis to clinical treatment and the integration of AI, robotics, 5G communications, and other frontier technologies to alter the concept 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 artificial intelligence and TCM is attracting increasing attention. 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.

(6) Brain-inspired intelligence research

From brain-inspired intelligence research, we can learn from the mechanisms by which the brain processes information. By simulating the dynamic evolution of brain neural systems and advanced cognitive functions, research teams can establish calculations and theoretical models with biological and mathematical foundations, develop a new generation of brain-inspired intelligence algorithms, achieve an intelligent system with the capacity to learn from self-experience, and apply the system to specific fields. Through brain–computer interaction, the algorithm will dynamically blend with individuals and groups of humans to build a brain–computer hybrid information processing terminal, and this will allow researchers to finally establish a new computing structure and

intelligent form to achieve intelligence augmentation and the application of group intelligence.

The key scientific issues include neuroscience theory, mathematical theory and methods, computer system architecture, and chip implementation. Specifically, these issues involve: 1) dynamic behavior analysis and data assimilation method of neuron biophysical impulse dynamics and axon-synaptic network mathematical models based on the knowledge of neuromorphology, neurophysiology, and multi-scale brain imaging data, 2) the non-Von Neumann computer architecture with communication as the core of computing–storage–communication integration and the high-speed adaptive routing communication system, and 3) new theories and novel methods in mathematical fields such as functional analysis, algebra, geometry, and computational mathematics for a multi-mode and multi-channel integrated intelligent system aiming at perception that is capable of judgment, decision-making, and control through the integration of memory, emotion, language, and rewards and punishments.

The European Union, the United States, and Japan conduct competitive research in this field through universities, research institutions, and companies based on state mandates. Supported by the "Human Brain Project," a research team at the University of Manchester has constructed a model known as Spinnaker using the Acorn RISC machine. The largest Spinnaker machine is capable of simulating one billion simple neurons. The US company IBM and the US Air Force have developed a chip named TrueNorth. This chip mimics the function of the human brain and can achieve the neuromorphic computation of 64 million neurons and 16 billion synapses. The American company Neuralink has developed practical brain–computer interface equipment and implanted brain surgery equipment.

Universities and research institutions in China, including Tsinghua University, Peking University, Zhejiang University, and Fudan University, initiated their brain-inspired intelligence research at a slightly later date compared to that of the international groups. The current study mainly focuses on visual/auditory chips and spiking neural network dynamics. However, we do possess state-of-the-art laboratory facilities for brain research and large-scale population sample data.

(7) Construction of the human single-cell atlas

Single-cell analysis primarily refers to the use of a digital matrix to systematically describe, classify, and integrate the gene expression characteristics of every single cell. The construction of the human single-cell atlas was based on single cell analysis in the human body. The present human cell atlas primarily relies on the transcriptome data of a single cell, and it still requires a series of -omics data, i.e., genome, proteome, and metabolome, to ensure data integration, visualization, and sharing. It is generally established that there are 30 trillion cells within the human body, and that the gene expression profile of these cells changes throughout the life cycle, thus contributing to the diversity of cell types and cell states and generating cell heterogeneity. Under normal circumstances, different types of cells work in concert in an orderly manner to perform the functions of tissues and organs. However, when stimulated by endogenous or exogenous environmental factors, more heterogeneous changes occur in the cells, ultimately leading to the emergence of pathological conditions and various diseases. Therefore, the information contained within the single cell atlas can more importantly be used to construct the single-cell atlas of diseases, particularly major diseases that seriously endanger human health.

Since 2016, researchers have completed the construction of human single-cell atlases of various organs and tissues, including the nervous system and immune system. In 2020, a team from Zhejiang University in China constructed a human cell atlas covering cells in both embryonic and adult stages from eight major systems to provide a foundation for the comprehensive identification and definition of normal and diseased cell types. Current and future research will establish a human cell atlas that integrates data from clinical observation, experimental research, and computational biology. Furthermore, it will be a space–time specific cell atlas that is associated with development and disease. Therefore, during the process of disease occurrence and development, the human single-cell atlas will provide a powerful means by which to identify novel disease biomarkers and to explore the network characteristics of molecular regulation of different cell types, cell states, and cellular interactions that are closely related to clinical therapeutics. The Human Tumor Atlas Network, a part of the National Cancer Institute Cancer Moonshot Initiative that was launched in 2016, aims to chart tumor transitions across space and time at a single-cell resolution. The construction of a complete human cell atlas will help us comprehensively decipher the dynamic process of prenatal and postnatal development, maturation,

aging, and disease transitions, particularly those involved in health and disease. In the near future, the construction of human single-cell atlas will allow researcher the opportunity to integrate information from multidisciplinary research, thus making it possible to investigate the entire process of life and disease thoroughly, variably, and three-dimensionally. It will reveal the individual and common pathogenesis of major human diseases to provide a foundation for clinically accurate diagnosis, personalized treatment, and targeted therapy. Finally, the human single-cell atlas exhibits the potential to be a prominent player in medicine in the era of great human health.

(8) The collection and use of real-world evidence to support drug research and clinical application

Real-world evidence refers to collected health care information outside of traditional clinical trials. Health care information can be derived from various sources, including, but not limited to, electronic health records, claims and billing data, product and disease registries, data gathered through personal devices, and data from observational studies. In December 2018, the US Food and Drug Administration (FDA) released a framework outlining how the FDA will evaluate real-world evidence intended to support the approval of a new indication for an approved drug or biologic or to help support or satisfy post-approval study requirements for drugs. In China, the National Medical Products Administration has also begun to explore this field. On January, 2020, it issued its first set of guidelines titled “Guiding Principles for the Development and Evaluation of Drugs Supported by Real-World Evidence (Trial)” that clarifies some basic definitions of real-world evidence such as research and data and clearly proposes the application of real-world evidence to support drug regulatory decisions to cover multiple links such as pre-market clinical research and development and post-market re-evaluation. Furthermore, “Guiding Principles for Real-World Data Used to Generate Real-World Evidence (Draft for Solicitation of Comments)” and “Technical Guidelines for the Development and Evaluation of Drugs for Children Supported by Real-World Research (Trial)” were successively issued in August 2020.

The value of real-world evidence is its potential for complementing the information gained from a traditional clinical trial. Although randomized, double-blind, clinical trials are regarded as the gold standard to evaluate the treatment efficacy and safety, they are known to possess limitations. real-world evidence, if of high quality, is expected to 1) provide evidence of the effectiveness and safety for the registration and marketing of new drugs, 2) provide evidence for modification of indications or safety information of approved drugs, 3) provide evidence for post-marketing study requirements or re-evaluation of drugs, and 4) guide the design and implementation of clinical trials.

Scientifically, internal and external validity is the ultimate goal of medical research. Randomized and controlled clinical trials (RCTs) exhibit the highest internal validity; however, they may be limited in external validity due to stringent inclusion and exclusion criteria. Conversely, real-world data are derived from multiple sources and diverse populations, thus extending their reach to broader populations. It is underscored that the process from real-world data to real-world evidence must be derived from sound research design and implementation, vigorous data cleaning and statistical analysis, and careful consideration and control of biases and confounding factors, as these are of particular concern for observational studies. Therefore, RCTs and real-world studies should be regarded as complementary. Observational real-world research alone cannot be used to draw definite conclusions; however, the results of these studies can complement RCTs and provide important insights for the design and implementation of subsequent RCTs. Technically, real-world data can be massive and messy. Based on this, it will be necessary to apply advanced and secure information technology to collect and store information and to apply advanced statistical methods, including machine learning, to integrate and analyze multi-dimensional and complex data.

Some legislative challenges are related to the policies and implementation of real-world evidence. In China, these challenges include 1) data acquisition and sharing, including administrative and geographical restrictions as well as many practical problems such as information security, usage rights, and ethics, 2) data quality, including the standards, integrity, accuracy, authenticity, and traceability of the data that must be integrated as a requirement and standard, 3) data management and analysis methods where for different types of data, continuous methodological innovation will be required, and 4) expertise, where scientists with expertise in this field and high-quality training programs will be critically needed.

(9) New target discovery and translation of active compounds in traditional Chinese medicine

The discovery of new active compounds in TCM involves using certain physical, chemical, and biological means to produce the desired biological phenotypes of drug-treated cells or animal models for exploration of new targets and target functions under the guidance of TCM. Meanwhile, research findings of new targets can be translated into clinical disease diagnosis, prevention and treatment, prognosis evaluation, and new drug development.

The key scientific issues include the existence of TCM as a complex system with the integrated regulation function of "multi-component, multi-pathway, and multi-target." These issues include the determination of active compounds in TCM and the selection of model target cells, the effective discovery and validation of new targets using interdisciplinary techniques, the relationship between new targets and disease models, and new target-based drug-forming and clinical application of active compounds. The aim of new target discovery is to identify active compounds in TCM that possess certain pharmacological activities. The correlation between new targets and disease phenotypes is the focus of this study. Further clinical translation of the new target for the treatment of diseases and the discovery of active compounds for these targets are the key points for drug development.

Recently, active compounds in TCM have been demonstrated to play important roles in the prevention and treatment of many diseases, including chronic and viral diseases, as they exhibit unique advantages. Research focused on the discovery of new targets based on the active compounds in TCM has been lagging; however, the identification of label-free drug targets by Mass Spectroscope-Cellular Thermal Shift Assay has rapidly developed and has attracted increasing attention. Additionally, the active compounds in TCM provide rich and valuable resources for modern drug research and development. The successful translation of these active compounds in TCM into innovative clinical drugs with clear targets and the classical advantages of TCM have become hot topics in modern Chinese medicine research.

(10) Pathogenesis, precision diagnosis, and treatment strategy of hereditary tumors in the Chinese population

Hereditary tumors represent a type of genetic disease caused by germline mutations of specific genes, and these tumors account for approximately 5%–10% of the tumors in humans. Many types of hereditary tumors exist, and complicated classification methods are currently available. The pathogenesis of hereditary tumors is still unclear. The "two-hit theory," "chromosomal imbalance hypothesis," and "single and multi-gene hypothesis" are generally recognized in academic circles. With the widespread use of next-generation sequencing technology, precise genetic detection provides a direction for the diagnosis of hereditary tumors and the development of new drugs and also provides more opportunities for individualized treatment.

The major scientific issues include using molecular biological methods to explore the genetic mechanisms underlying tumorigenesis and development. Moreover, these issues also include identifying unknown genetic susceptibility genes and clarifying the value of variants of uncertain significance. Multidisciplinary collaboration for comprehensive data analysis promotes the development of precise molecular pathology, thus allowing for the construction of a complete clinical and genetic information database. Additionally, it is also used explore a comprehensive map of hereditary tumor families, analyze the correlation between genotype and phenotype, screen existing hereditary tumors for key variant genes, determine new applications for old drugs, and develop new molecular targeted drugs. Approximately 50% or more of patients or families who meet the clinical diagnosis do not exhibit a clear molecular pathogenesis. Large-scale genome-wide association studies are required to determine new susceptible loci. Compared to common hereditary tumors, the etiology of rare hereditary tumors is more complex, and the research is relatively lagging. It is essential to identify commonly mutated genes in patients and to reveal the mechanism underlying the pathogenesis of these rare hereditary tumors. The standard use of gene testing technology combined with genetic counseling in genetic risk assessment, early screening, molecular diagnosis, risk management, long-term follow-up, and other cancer cycle management strategies is particularly significant in the advancement of research on hereditary tumors.

In the Chinese population, mutation identification and accurate treatment of hereditary tumors have commenced; however, there are still some limitations that include a lack of core guidelines and an inadequate consensus for genetic consultation, a limited understanding of pathogenesis, and a delayed advancement of corresponding molecular targeted drugs. Presently, based on genome research and

systematic genetic screening in China and abroad, several pathway changes driven by key gene abnormalities have been detected, and rationally designed treatment strategies for tumors with gene mutations, including inducing ferroptosis, promoting oxidative stress, and metabolic changes have been implemented. A favorable response of certain hereditary tumors to immunotherapy is also a major direction of treatment. With the in-depth study of molecular biological characteristis of hereditary tumors, these treatment strategies are constantly being improved. In the future, it will be necessary to consider the application of experimental treatment strategies into clinical practice, particularly the possible precise gene-editing technology that may become available in the future to prevent the onset of hereditary tumors.

1.2 Interpretation for three key engineering research fronts

1.2.1 Improving public health and epidemic prevention systems and emergency mechanisms

Public health involves organizing the community to improve environmental sanitation conditions, prevent and control the spread of diseases, develop good hygiene and a civilized way of life, and provide medical services to prevent diseases and promote the health of the people. Public health requires collective, cooperative, and organized actions as well as sustainable policies to improve the health of the entire population and reduce health inequality. Public health and epidemic prevention systems and emergency mechanisms primarily refer to the institutions, personnel, and management operating mechanisms in place for the prevention and control of traditional and emerging infectious diseases and to the mechanism for joint response in the event of a public health emergency by allowing for the deployment of medical and health resources. The disease control system is an important component of the public health service system, and is also the main provider of national public health services and health protection for the people. The scope of this system includes environmental health, control of infectious and non-communicable diseases, individual health education, organization of early diagnosis and treatment of diseases, and development of social systems to ensure that all individuals enjoy a healthy status of living and achieve healthy production and longevity throughout their entire lives.

A modern public health and epidemic prevention system should include prevention-oriented ideology, a clear management system of powers and responsibilities, a unified and efficient emergency command and dispatching work mechanism, a strong legal protection system, a well-trained expert team system, a meticulous complete disease monitoring system, an accurate laboratory testing technology system, a rapid response and guarantee system, a scientific and advanced information system, and a practical public health service system.

In response to COVID-19, China has undertaken powerful measures and demonstrated excellent leadership, response ability, organization and mobilization ability, and implementation ability. However, this prevention and control exercise also exposes the deficiencies of the infectious disease prevention and control system and the health emergency mechanism in China. These deficiencies include an outdated concept and model of epidemic early warning, insufficient coordination of medical treatment, disease prevention and control, and medical security, an insufficient application of modern technology in professional institutions of public health, and an unclear legal status for health technology departments.

The key scientific issues for improving the public health epidemic prevention system and emergency response mechanism include 1) improving domestic and international public health-related laws and regulations in China, enhancing the feasibility and scientific nature of the legalization of epidemic prevention and control, actively participating in global prevention and control actions and health emergencies, and promoting the improvement of the leadership and resource coordination capabilities of the World Health Organization (WHO); 2) improving the public health management system that combines general situations and emergencies, establishing a scientifically standardized approach to prevent and control the spread of infectious disease, and establishing a unified emergency command and dispatch system, and improving a unified public health guarantee system; 3) establishing a multi-point trigger mechanism and a multi-channel surveillance mechanism and early warning mechanism for infectious diseases, establishing an online platform for multidisciplinary data sharing, improving the ability of infectious disease surveillance and early warning, and scientific nature and efficiency of decision-making about public health emergencies; 4) realizing the

modernization of infectious disease prevention and control and health emergency technology and combining traditional theoretical knowledge with information technology, AI, big data, and other technologies. The research hotspots include 1) reformation of the medical treatment system for major epidemics, 2) grass-root infectious disease prevention and control capacity building, 3) measures and policies regarding public health emergencies and epidemic prevention and control policies, 4) comparison of the prevention and control measures for infectious diseases in various countries, and 5) construction of a national public health safety system.

When focusing on core papers, the top 10 countries in this research front of "improving public health and epidemic prevention systems and emergency mechanisms" are from North America, Europe, Asia, and Africa. Among them, the United States, the United Kingdom, and China are the top three (Table 1.2.1), where the United States accounts for 57.50%, and China and the United Kingdom eaeh account for greater than 10% of the published papers. The number of papers contributed by Chinese authors is second only to that of the United Kingdom, and the average citation frequency is 14.71, indicating that there is still room for improvement. From the cooperation network of core paper-generating countries, the top 10 countries with respect to the number of core papers have cooperative relations (Figure 1.2.1). Among the top 10 institutions with greatest output of core papers on "improving public health and epidemic prevention systems and emergency mechanisms", three were from the United States, three were from the United Kingdom, two were from Africa, one was the WHO, and one was from China. Among the institutions, the top three institutions are US Centers for

Table 1.2.1 Countries with the greatest output of core papers on "improving public health and epidemic prevention systems and emergency mechanisms"

No.	Country	Core papers	Percentage of core papers	Citations	Citations per paper
1	USA	138	57.50%	1 674	12.13
2	UK	29	12.08%	644	22.21
3	China	28	11.67%	412	14.71
4	Australia	16	6.67%	294	18.38
5	Switzerland	16	6.67%	398	24.88
6	France	13	5.42%	302	23.23
7	Netherlands	10	4.17%	238	23.80
8	Germany	9	3.75%	152	16.89
9	Sierra Leone	9	3.75%	107	11.89
10	Italy	7	2.92%	118	16.86

Figure 1.2.1 Collaboration network among major countries in the engineering research front of "improving public health and epidemic prevention systems and emergency mechanisms"

Disease Control and Prevention, Harvard University, and WHO; and Fudan University ranks 10th based on the number of papers published (Table 1.2.2). The cooperation network chart for the top 10 core paper producers indicates that cooperation exists among these institutions (Figure 1.2.2).

1.2.2 Global research on COVID-19 and emerging highly pathogenic viruses

The SARS-CoV-2 is currently the seventh known coronavirus that is pathogenic to humans. A large number of other coronaviruses also exist in nature. To cope with the threat of the COVID-19 pandemic, we aimed to systematically study the viral proliferation and infection, and mechanism underlying the pathogenesis of COVID-19, to explore the features of transmission, epidemiology, and outbreak, to elucidate the origin, evolution, and mutation, and to develop vaccines and medicines to allow for the safe and efficient treatment of this disease and ultimately provide scientific support for the prevention and control of the pandemic. Through the collaboration of scientists throughout the world, major progress has been made with respect to the basic knowledge and application research of SARS-CoV-2, and the knowledge gained from these studies has profoundly deepened our understanding of the virus and the diseases caused by it. In particular, Chinese scientists identified SARS-CoV-2 as the pathogen underlying this disease very rapidly, and they determined the full genome sequence of this virus and shared it with the world. Chinese scientists have demonstrated that SARS-CoV-2 can be transmitted via human to human

Table 1.2.2 Institutions with the greatest output of core papers on "improving public health and epidemic prevention systems and emergency mechanisms"

No.	Institution	Core papers	Percentage of core papers	Citations	Citations per paper
1	US Centers for Disease Control and Prevention	65	27.08%	718	11.05
2	Harvard University	18	7.50%	512	28.44
3	WHO	18	7.50%	447	24.83
4	Johns Hopkins University	9	3.75%	37	4.11
5	University of Oxford	8	3.33%	292	36.50
6	London School of Hygiene & Tropical Medicine	6	2.50%	236	39.33
7	Ministry of Health & Sanitation-Government of Sierra Leone	5	2.08%	73	14.60
8	Aix-Marseille University	4	1.67%	178	44.50
9	Ministry of Health, Republic of Liberia	4	1.67%	51	12.75
10	Fudan University	4	1.67%	18	4.50

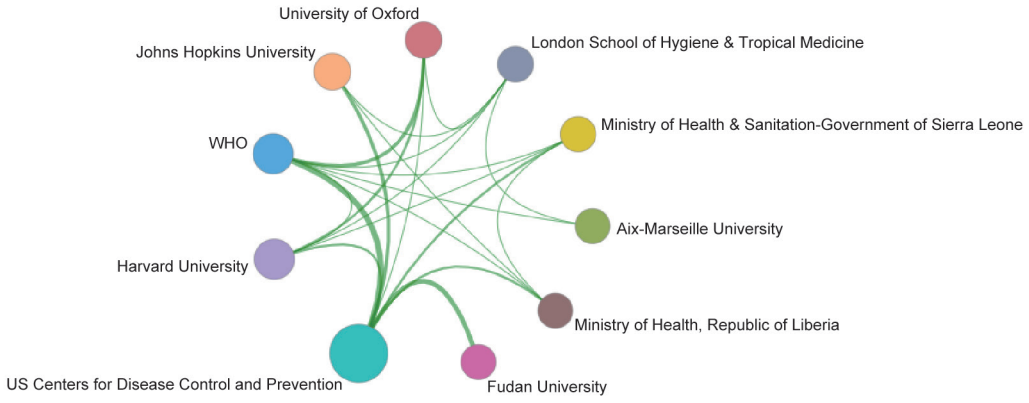

Figure 1.2.2 Collaboration network among major institutions in the engineering research front of "improving public health and epidemic prevention systems and emergency mechanisms"

transmission. The structures of the SARS-CoV-2 and their key coding proteins have been resolved rapidly. Reliable cell and animal models have been established for further research and development of vaccines and pharmaceuticals. Several vaccines and therapeutic drugs are undergoing phase III clinical trials. The domestic contagion was effectively controlled in a very short period of time. All of these achievements have embodied the strength of Chinese science and technology.

The critical scientific issues regarding global research on the SARS-CoV-2 and emerging highly pathogenic viruses include a lack of clarity regarding the molecular mechanism underlying interspecies transmission of the SARS-CoV-2 in humans, poor knowledge regarding the distribution, evolution, and recombination/mutation of coronaviruses derived from different animals in the natural ecological system, and a lack of clarity regarding the key stages in the viral life cycle, including replication, translation, assembly, and release. The structures and functions of the viral genome and the encoded proteins of the SARS-CoV-2 and other emerging highly pathogenic viruses remain to be determined through the use of structural biology, bioinformatics, and molecular biology technologies. Additionally, mechanisms by which the immune system is activated after viral infection and the pathogenesis of acute lung injury and multi-organ failure remain to be investigated. Specific diagnostic markers, risk factors for severe disease, and correlates for immune protection remain to be determined. Novel findings from basic researchers and clinical discoveries are required for more effective clinical guidance.

Global research on SARS-CoV-2 and emerging highly pathogenic viruses focuses on 1) the origin, evolution, and genetic mutation of coronaviruses derived from animals; 2) the structures, and function of the genome and encoded proteins of SARS-CoV-2; 3) the clinical manifestations, diagnosis, and management of diseases caused by the SARS-CoV-2; 4) the mechanism of immune protection and pathological damage; 5) the transmission pattern and the intervention strategies applied; 6) the mechanism of immune protection and the development of vaccines; and 7) the screening and evolution of anti-virus pharmaceuticals. In general, future research will rely on a more integrated application of single-cell sequencing, systems biology, reverse genetics, big data, and AI for further investigation of the infection, pathogenesis, and transmission of SARS-CoV-2. A greater number of next-generation vaccines and drugs based on rational design will enter clinical trials in the near future. More precise protection and control and also the management concept will be verified in practice.

When focusing on core papers, the top five countries in the research front involving “global research on COVID-19 and emerging highly pathogenic viruses” are the United States, China, the United Kingdom, Germany, and France (Table 1.2.3). In terms of the citation frequency for each article, the research content of this front is the focus of attention, and the citation frequency of core papers is very high. Cooperation network of the core paper-producing countries revealed that the top 10 countries in the number of core papers possess close cooperative relations (Figure 1.2.3). The top 10 institutions publishing the highest number of core papers were the US Centers for Disease Control and Prevention (USA), the Chinese Academy of Sciences (China), Harvard University (USA), the University of Hong Kong (China), the National Institute of Allergy and Infectious Disease (USA), the University of Texas Medical Branch (USA), the University of Oxford (UK), Huazhong University of Science and Technology (China), the University of North Carolina (USA), and Fudan University (China) (Table 1.2.4). The collaboration network of the top 10 core paper-producing institutions reveals that a number of institutions have developed mutual collaborations (Figure 1.2.4). The above analysis reveals that China is on the same line with international peers in the research frontiers of the global study on SARS-CoV-2 and potential highly pathogenic viruses, and advances in pathogen identification and animal models. Nevertheless, the research team in China remains limited, and comprehensive international collaboration should be encouraged.

1.2.3 Gut microbiota imbalances and diseases

Research examining gut microbiota imbalances and diseases has enhanced the traditional understanding of major diseases such as infections, liver disease, tumors, and metabolic diseases in medicine, and the findings from these research projects have facilitated revolutionary changes in the prevention, diagnosis, and treatment of various diseases. The occurrence and development of diseases are both primarily related to immunity and metabolism. The gut is one of the largest immune and metabolic organs. Gut microbes and their products can directly or indirectly affect the occurrence, development, and prognosis of disease through

Table 1.2.3 Countries with the greatest output of core papers on “global research on COVID-19 and emerging highly pathogenic viruses”

No.	Country	Core papers	Percentage of core papers	Citations	Citations per paper
1	USA	1 309	48.36%	92 353	70.55
2	China	650	24.01%	64 924	99.88
3	UK	348	12.86%	31 554	90.67
4	Germany	249	9.20%	22021	88.44
5	France	217	8.02%	22 860	105.35
6	Canada	161	5.95%	16 315	101.34
7	Italy	154	5.69%	14 037	91.15
8	Brazil	148	5.47%	17 307	116.94
9	Switzerland	137	5.06%	15 805	115.36
10	Netherlands	122	4.51%	12 971	106.32

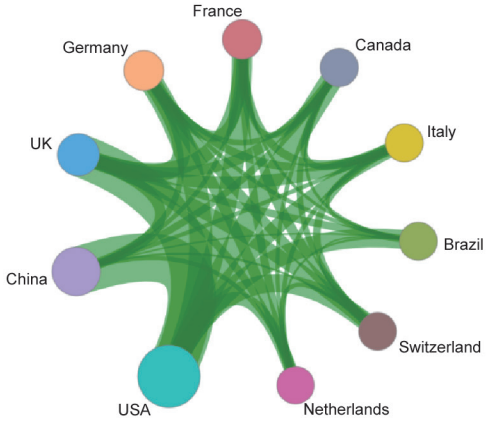

Figure 1.2.3 Collaboration network among major countries in the engineering research front of “global research on COVID-19 and emerging highly pathogenic viruses”

Table 1.2.4 Institutions with the greatest output of core papers on “global research on COVID-19 and emerging highly pathogenic viruses”

No.	Institution	Core papers	Percentage of core papers	Citations	Citations per paper
1	US Centers for Disease Control and Prevention	233	8.61%	28 131	120.73
2	Chinese Academy of Sciences	127	4.69%	24 128	189.98
3	Harvard University	100	3.69%	12 249	122.49
4	The University of Hong Kong	92	3.40%	11 535	125.38
5	National Institute of Allergy and Infectious Disease	88	3.25%	6 931	78.76
6	University of Texas Medical Branch	88	3.25%	5 448	61.91
7	University of Oxford	75	2.77%	10 257	136.76
8	Huazhong University of Science and Technology	71	2.62%	13 079	184.21
9	University of North Carolina	70	2.59%	10 201	145.73
10	Fudan University	64	2.36%	8 696	135.88

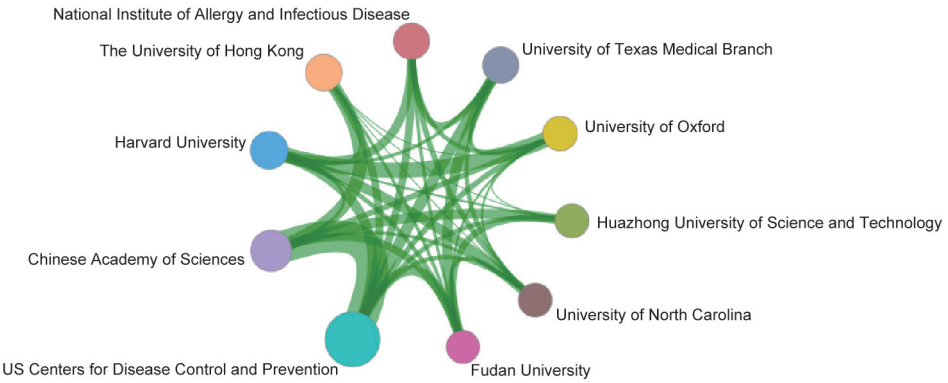

Figure 1.2.4 Collaboration network among major institutions in the engineering research front of "global research on COVID-19 and emerging highly pathogenic viruses"

the gut. Under the influence of the external environment, the microbiota balance between normal microbes and/or between normal microbiota and their host changes from a physiological combination to a pathological combination. In recent years, studies have found that gut microbiota imbalances play an important role in the occurrence and development of infection, tumors, cardiovascular disease, liver disease, obesity, diabetes, inflammatory bowel disease, autoimmune disease, and nervous system diseases, which led to new breakthroughs in the pathogenesis of major diseases. At the same time, new diagnostic methods based on changes in gut microbiota have provided new directions for the rapid and accurate diagnosis of conditions such as unexplained infections and difficult and complicated diseases. Additionally, gut microbiota regulation can be used as a strategy to prevent and treat many difficult-to-treat diseases, including *Clostridium difficile* infection and inflammatory bowel disease. Furthermore, research focused on gut microbiota imbalances and disease has provided new targets and new approaches for drug application. The efficacy and treatment successes or failures of many oral and injection drugs are closely related to the composition and function of the gut microbiota. Moreover, research examining gut microbiota and disease has opened up a new field interpreting the mechanism of action of TCM in China.

Research examining gut microbiota and diseases has attracted a great deal of attention from governments, scientific and technological circles, enterprises, and the public. Developed countries regard it as an important field to be developed under national science and technology strategic planning. Since the establishment of the "Human Microbiome Project" and "Metagenomics of the Human Intestinal Tract Consortium" in 2008, as well as the establishment of the National Microbiome Initiative in the United States in 2016, many countries throughout the world have established dozens of large-scale "microbiome" programs with billions of dollars invested in gut microbiota and their role in health and diseases. Many key deployments have been made in the fields of gut microbiota imbalances and major diseases, microbiota and biosafety, and the clinical application of microbiota. It is hoped that through basic research in these fields, major scientific issues associated with gut microbiota can be solved and that the development of the entire related medicine, machinery, and information industry will be promoted.

Currently, the key scientific issues in studying gut microbiota imbalances and diseases include integrating the theoretical basis (i.e., life science, modern medicine, and information science) and technical means from the perspective of the interaction mechanism between gut microbiota and human body; revealing the causal relationship and mechanism between the occurrence and development of diseases and gut microbiota imbalance; and accurately mining early warning, prediction, diagnosis and treatment target of diseases based on gut microbiota. Additionally, we should systematically research and develop new drugs and technologies to correct the imbalances in gut microbiota to prevent the occurrence and development of diseases.

The overall development trend extends from research examining the changes in gut microbiota structure and function in the process of disease occurrence and development and its correlation with diseases to research on the causal mechanism of gut microbiota changes and

disease occurrence and development in combination with the development of related drugs and therapies. Research hotspots include 1) the role of gut microbiota imbalances in the occurrence and development of diseases and their association with diseases; 2) mechanism underlying gut microbiota imbalance and disease occurrence and development; 3) disease diagnosis and treatment target mining based on gut microbiota imbalance; 4) immunological mechanism and clinical application of the influences of gut microbiota on disease treatment effects; 5) the effect of gut microbiota on the metabolism and efficacy of oral drugs and the underlying mechanism; and 6) new drugs, strategies, and methods to correct the imbalance in gut microbiota.

Among the top 10 countries producing core papers focused on "gut microbiota imbalances and diseases," the United States is clearly in the leading position and accounts for 50.25% of these papers. China and France ranked second and third with respect to the number of core papers, accounting for 16.75% and 13.20%, respectively. The citation frequency of the core papers in this research front was 117.67–209.33 (Table 1.2.5), and the citation frequency of Chinese core papers was 138.00, indicating that the influence of the research work of Chinese scholars in this front still has room for improvement. The cooperation network of core paper-producing countries reveals that the top 10 countries generating the most number of core papers have cooperative relations within a certain range (Figure 1.2.5). Among the top 10 institutions that published core papers focused on "gut microbiota imbalance and disease," the top three institutions were Harvard University, French National Institute for Agricultural Research, and the University of California San Diego. The Chinese Academy of Sciences and Shanghai Jiao Tong University ranked 7th and 9th in this list (Table 1.2.6). The cooperation network of the top 10 core paper producing institutions reveals a cooperation among these institutions (Figure 1.2.6). The above analysis revealed that China is at par with foreign countries in the engineering research front of "gut microbiota imbalances and diseases."

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, including the fields of basic medicine, clinical medicine, pharmacy, medical informatics and biomedical engineering, public health, and preventive medicine. The three emerging fronts are "human organoids-on-a-chip technology", "5G+ health care", and "human microbiome diagnostic prevention and intervention". Traditional research has focused on the "development of vaccines and drugs for major infectious diseases", "development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases", "small molecule discovery in cancer immunotherapy", "research and development of new antibiotics, artificial intelligence-based clinical decision support systems", "off-target effects and their

Table 1.2.5 Countries with the greatest output of core papers on "gut microbiota imbalances and diseases"

No.	Country	Core papers	Percentage of core papers	Citations	Citations per paper
1	USA	99	50.25%	16 866	170.36
2	China	33	16.75%	4 554	138.00
3	France	26	13.20%	4 468	171.85
4	Canada	15	7.61%	3 140	209.33
5	Spain	15	7.61%	2 217	147.80
6	Belgium	14	7.11%	2 217	158.36
7	Sweden	12	6.09%	2 260	188.33
8	Japan	12	6.09%	1 412	117.67
9	Germany	11	5.58%	2 046	186.00
10	Denmark	10	5.08%	2 326	232.60

Figure 1.2.5 Collaboration network among major countries in the engineering research front of “gut microbiota imbalances and diseases”

Table 1.2.6 Institutions with the greatest output of core papers on “gut microbiota imbalances and diseases”

No	Institution	Core papers	Percentage of core papers	Citations	Citations per paper
1	Harvard University	16	8.12%	3 035	189.69
2	French National Institute for Agricultural Research	11	5.58%	2 713	246.64
3	University of California San Diego	9	4.57%	1 881	209.00
4	University of Copenhagen	8	4.06%	2 118	264.75
5	Emory University	8	4.06%	1 831	228.88
6	Broad Institute	8	4.06%	1 812	226.50
7	Chinese Academy of Sciences	7	3.55%	1 362	194.57
8	Baylor College of Medicine	7	3.55%	951	135.86
9	Shanghai Jiao Tong University	7	3.55%	724	103.43
10	French National Institute of Health and Medical Research	6	3.05%	1 545	257.50

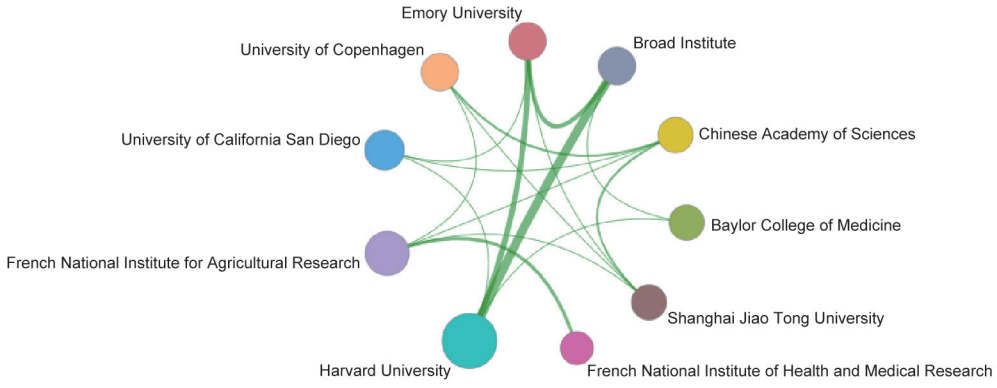

Figure 1.2.6 Collaboration network among major institutions in the engineering research front of “gut microbiota imbalances and diseases”

countermeasures", and "chimeric antigen receptor-modified T (CAR-T) treatment technology for solid tumors" (Table 2.1.1). All patents related to these 10 fronts published between 2014 and 2019 have been listed in Table 2.1.2.

(1) Development of vaccines and drugs for major infectious diseases

A major infectious disease outbreak can occur in a short time period and can affect a wide range of individuals and ultimately cause a large number of infections and/or deaths. Such an outbreak of emerging acute infectious diseases or diseases of unknown origin that poses a major threat to human health, seriously affects social stability and requires emergency management. The incidence of major infectious diseases is far more common than that of diseases that occur perennially.

As the COVID-19 epidemic continues to spread in 2020, there is an urgent need for drugs and vaccines for controlling and treating SARS-CoV-2 infections in a global scale. As "globalization" allows more infectious diseases to spread more rapidly, further and more detail-oriented development of vaccines and drugs targeting major infectious disease has become a necessity. Some key technical challenges in the development of vaccines and drugs for major infectious diseases include the ability to quickly detect and clarify unknown pathogens, a means by which to search for a safe and effective vaccine type for a certain disease, methods to overcome the problem of genetic variation of pathogens,

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	Development of vaccines and drugs for major infectious diseases	2 537	30 145	11.88	2014.6
2	Development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases	842	7 777	9.24	2015.6
3	Human organoids-on-a-chip technology	108	463	4.29	2017.1
4	Research and development of new antibiotics	600	3 093	5.16	2015.2
5	Small molecule discovery in cancer immunotherapy	1 918	31 621	16.49	2014.7
6	5G+ health care	326	5 256	16.12	2015.9
7	Artificial intelligence-based clinical decision support systems	6 416	26 796	4.18	2017.6
8	Off-target effects and their countermeasures	196	2 947	15.04	2017.4
9	CAR-T treatment technology for solid tumors	1 764	16 923	9.59	2017.0
10	Human microbiome diagnostic prevention and intervention	2 754	31 741	11.53	2014.6

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	2014	2015	2016	2017	2018	2019
1	Development of vaccines and drugs for major infectious diseases	160	187	291	353	384	352
2	Development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases	40	60	103	163	156	150
3	Human organoids-on-a-chip technology	6	9	10	19	29	28
4	Research and development of new antibiotics	74	54	66	66	101	100
5	Small molecule discovery in cancer immunotherapy	167	205	236	226	280	274
6	5G+ health care	21	22	38	45	60	80
7	Artificial intelligence-based clinical decision support system	185	248	398	771	1524	2924
8	Off-target effects and their countermeasures	11	14	15	35	54	62
9	CAR-T treatment technology for solid tumors	57	83	203	344	393	549
10	Human microbiome diagnostic prevention and intervention	215	236	274	370	393	419

means of coping with or avoiding pathogen drug resistance, and techniques to achieve high efficiency in monitoring and management of suspected infectious disease spread.

(2) Development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases

Major emerging and re-emerging emergency infectious diseases refer to infectious diseases caused by new species or new pathogenic microorganisms and also to reoccurring ancient infectious diseases that seriously affect the social stability and pose a major threat to human health. The development of diagnostic reagents and equipment for major emerging and re-emerging infectious diseases is of great significance in the field of disease prevention and control, as it can affect health, economic development, and social stability. Due to economic integration and globalization, human habitat urbanization, large-scale application of living utilities, and the popularity of modern transportation, especially railways and flights, infectious diseases now occur more frequently and spread more rapidly. To respond to major emerging and re-emerging infectious disease emergencies in a timely and effective manner, the global demand for diagnostic reagents and equipment is continuously growing.

Presently, the development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases depends on solving the following key technical problems: collecting pathogen strains from different regions—local and non-local—to enrich the pathogen source library and gene information databases; providing a prerequisite for the rapid identification and genetic variation monitoring of the pathogens responsible for causing emerging and re-emerging emergency infectious diseases; developing key technical components of equipment to improve the testing speed, through-put, and sensitivity of equipment; promoting the function integration, miniaturization, and portability of equipment in order to fulfill the different practical requirements associated with centralized detection and individual detection in different scenarios; and performing innovative research on the key components of diagnostic reagents and the principles of testing methods to improve testing sensitivity and specificity.

(3) Human organoids-on-a-chip technology

Human organoids-on-a-chip represents a three-dimensional culture technology based on microfluidic chip platforms to induce pluripotent cells to differentiate into cell clusters and tissues *in vitro*. This technology aims to form spatial structures similar to the tissue sources on the chip by simulating and controlling biological behaviors of the cell clusters and to further reproduce crucial functions to achieve values in drug screening and evaluation, genetic disease modeling, cell therapy, and various biomedical applications. Although research focused on organoids-on-a-chip is still in its initial stages, it has been highly valued due to the vast potential and development prospects of these platforms. Current topics of interest focus on the following aspects: 1) intelligent biomaterials; 2) interaction between substrates and cultured cell clusters; 3) co-culture systems; 4) organoid real-time monitoring; 5) internal micro-environmental regulation; 6) connection and cooperation of multiple organoids-on-chips; 7) drug screening, toxicity classification, and model establishment.

(4) Research and development of new antibiotics

Antibiotics are chemical substances naturally produced by a living organism, typically microbes, which are resistant to pathogens or other substances. Antibiotics control the growth and division of competing microorganisms or cause death by interfering with critical biological processes, such as synthesis of nucleic acids, proteins, and cell walls, or with membrane integrity and permeability. However, antimicrobial resistance (AMR) occurs when pathogenic bacteria develop the ability to escape from the selective pressure exerted by antibiotics that are designed to inhibit their growth or kill them.

Due to the rapid emergence of AMR, there is a growing need to discover new antibacterial agents to address the shortages within the clinical arsenal. However, our technologies and the ability to discover antibiotics from environmental microbes remain inadequate. Additionally, antibiotic complementary and alternative therapies such as antibiotic adjuvants, anti-virulence strategies, phage therapy, and methods to regulate human microbial flora are still in the early stages of proof-of-concept. Due to the shortage of available targets and chemical spaces, there are numerous problems in the discovery, design, synthesis, and optimization of new antibacterial agents, particularly those with novel modes of action. The clinical application of antibacterial agents has enabled numerous complicated medical methods to become successfully realized and to even become routine. However, the increasing problems raised by AMR bring global challenges to curing

infections. The development of new antibacterial agents could help to overcome multidrug-resistant bacteria-induced problems such as a lack of effective anti-infectious drugs, increased mortality, and high medical expenses.

The contradiction with the increasing multi-drug resistant strains is that the enthusiasm for developing new antibacterial drugs is extremely low. One major reason is that generic antibiotics are still effective for treating many infections, and this results in low profits. Additionally, the uncoordinated costs of investment and return have caused many big pharma companies to leave this field. Repairing the AMR and antibacterial pipelines is a comprehensive problem that requires joint support from multiple directions that include novel methods for antibiotic discovery, appropriate clinical usage of antibiotics, drug development and regulation, and increasing financial support and business. In the era of bacterial resistance, the ideas regarding anti-infection agents would switch from broad-spectrum to narrow-spectrum agents based on thorough comprehension of the bacteria and pathogenesis and on the interaction with the host. Additionally, the international community should extensively investigate any strategies that can serve complementary to antibiotics, combination therapy, and rapid and accurate diagnosis of bacterial infections. These transformations will greatly broaden the target diversity of antibacterial agents, open new avenues to extend the clinical life of antibiotics, and eventually overcome the rapid emergence of AMR.

(5) Small molecule discovery in cancer immunotherapy

Small-molecule drugs in tumor immunotherapy target the innate immune system or the tumor immune microenvironment and act on natural/adaptive immune cell molecules or pathways to relieve tumor immunosuppression and restore the anti-tumor immunity within the body. Immunotherapy based on small molecules can offer compensation for the limited bio-distribution of macromolecules, improve antitumor efficacy, and reduce systemic immune toxicity, which will be the primary research and development direction of future immunotherapy. Small-molecule drugs targeting immunotherapy can be administered in an “on/off” manner over time to achieve precise control of efficacy and toxicity. In contrast to the high specificity of monoclonal antibodies, small-molecule drugs non-specifically bind to cells and molecules with low oral bioavailability and uneven distribution to affect the pharmaceutical properties of the compound. Small-molecule drugs can easily enter cells, target different immune cells, and induce various immune effects. Thus, small changes in molecular structure may lead to tremendous variations in efficacy and toxicity. There is an urgent need to simulate the interaction between diverse molecular structure and the activation or inhibition targets in immune cells. Additionally, the efficacy and toxicity of these drugs must be clearly delineated as indicated in the “immunological small molecule drug structure-effect diagram.” Compared to immunotherapy based on biological antibodies, oral small molecules can more easily enter the tumor microenvironment and can simultaneously act on intracellular and external targets to enhance the anti-tumor efficacy. Screening for small-molecule drugs that cross certain physiological barriers, such as the blood-brain barrier, can benefit more cancer patients. Additionally, small-molecule immunotherapy can also provide the best pharmacokinetic and pharmacodynamic parameters, thus effectively avoiding immune-related adverse events caused by the systemic immunogenicity of monoclonal antibodies. Small molecule drugs used alone or in combination with monoclonal antibodies can solve the problem of low clinical response and drug resistance. Accordingly, small-molecule immunotherapy is expected to play a comprehensive role in mediating anti-tumor immunity. Following the development of monoclonal antibody immunotherapies, significant progress has been achieved in small-molecule immunotherapy in recent years. Tremendous breakthroughs have been achieved in small molecule immunotherapy and have allowed for the targeting of PD-1/PD-L1, IDO, STING, TLR, A2A, and other newly discovered co-suppression and co-stimulation targets. Moreover, small molecule drugs targeting PD-1/PD-L1, IDO-1, and STING have successively entered clinical trials. As no small-molecule immunological drugs have been approved to date, future research will continue to focus on discovering new small molecules with particular chemical types and higher potency in an attempt to identify biomarkers that can accurately classify patients.

Given their low production and development costs, small-molecule drugs are expected to benefit cancer patients to a greater extent. Small molecule immunotherapy can be combined with biological agents or traditional cancer therapies such as immune checkpoint inhibitors, targeted therapy, or chemotherapy to enhance the anti-tumor efficacy and to provide inherent advantages over biological

immunotherapy that include a wider range of molecular targets and lower rates of immune-related adverse events. By exploring the molecular mechanism of small-molecule immunotherapy and optimizing the strategies and timing of small-molecule drug combination therapy to maximize its effect, we can achieve effective transformation from basic discovery to clinical application and open a new chapter in tumor immune precision therapy.

(6) 5G+ health care

Emerging 5G+ healthcare is based on the high speed, low latency, low power consumption, and large capacity of 5G technology (i.e., the fifth-generation mobile communication technology), and it allows for full use of the advantages of medical technology in large hospitals as it allows them to focus on providing digital, mobile, and remote health and medical services in pre-diagnosis and during and after diagnosis. This emerging 5G+ health care uses Internet terminals, such as smartphones, tablets, Virtual reality/augmented reality, wearables, and multimedia communication devices; and intelligent medical equipment, such as surgical robots, medical imaging equipment, and *in vitro* diagnostic equipment that is linked to the 5G medical private network composed of networks, such as wireless access networks, bearer networks, and core networks. The real-time, dynamic, and continuous monitoring of vital sign data, such as blood pressure, blood glucose, and heart rate; and remote transmission and access of image data can all be realized Examination reports, electronic medical records, and ultra-high-definition long-distance communications, such as video calls and real-time information feedback are performed smoothly to allow for real-time and high-quality interaction between doctors and patients and among the doctors themselves. The application of 5G+ health care is becoming increasingly extensive, and 5G+ health care is gradually taking shape and maturing. The first example is medical monitoring and nursing applications based on the wireless monitoring of medical equipment data, including mobile infusion, mobile care, and patient positioning. The second example is medical diagnosis and guidance applications based on video and image interaction, such as mobile rounds, remote diagnosis, remote consultation, and mobile-first aid. The third example is remote control applications based on video and force feedback, such as remote robotic ultrasound inspection, robotic endoscopy, and remote robotic surgery. 5G+ health care is an important part of future health care. Countries with a strong information infrastructure are racing to increase investments in 5G+ health care standards, technology, and applications. The sustainable development of 5G+ health care is inseparable from the construction of the 5G private medical network, the iteration of smart mobile terminals, and the innovation of smart medical equipment. It will be promoted through further integration with big data, the Internet of Things, robotics, artificial intelligence, and other new technologies. The healthcare industry continues to develop and evolve towards wireless, intelligent, and fully connected service to provide patients with high-quality, efficient, and convenient healthcare services, ultimately improving the health of the population.

(7) Artificial Intelligence-based clinical decision support system

Artificial intelligence-based clinical decision support system (AI-CDSS) refers to an information system that assists healthcare providers with comprehensive analysis and judgment decisions by applying the artificial intelligence technology along with their comprehensive clinical knowledge and the subjective and objective conditions of patients. AI-CDSS aims to enhance the accuracy, individualization, and efficiency of clinical decision-making and actions by reinforcing the medical intervention ability, thus improving healthcare quality and capability. AI-CDSS primarily extracts the potential connections and knowledge from structurally diverse medical big data, such as pictures, videos, and texts, through the use of technologies, such as natural language processing, knowledge engineering, computer vision, machine learning, and others to integrate with biomedical technologies to further construct the clinical diagnosis and deduction logic, classifications, and prediction models. The developed system or model is integrated into the clinical information system and embedded into the diagnosis or treatment process to provide enhanced decision support abilities in medical practice. AI-CDSS can be applied throughout the diagnosis process, including during the analysis and processing of disease information, the prediction of disease risks, the intelligent diagnosis support of disease, the guidance of medication use, the assistance with the treatment, the prevention and prognosis of disease for patients, and other tasks. Currently, it is the most widely used tool in specialization-oriented intelligent diagnosis support in rheumatoid arthritis, cancer, lung disease, heart disease, diabetic retinopathy, hepatitis, Alzheimer's disease, liver disease, dengue fever,

and Parkinson's disease. In 2016, the global market value of the clinical decision support system was 79 million USD, and it is estimated to increase to 1.76 billion USD by 2023. AI-CDSS is not only the core developmental direction of CDSS, but it also represents the key position of artificial intelligence applications in healthcare. In the context of global ageing and insufficient medical resources, AI-CDSS is regarded as an important approach to supplement medical resources and to improve service quality and efficiency, and has already become an essential component of the medical industry worldwide. To construct reliable and sustainable AI-CDSS, standardized expression of complicated medical knowledge, integration of multi-source knowledge, and semantic normalization of data are the foundations that must be developed. Additionally, to improve the interpretability and transportability of the system, the development of multi-modal data and multi-disciplinary clinical decision support abilities are important directions for AI-CDSS. With the increased involvement of AI in clinical diagnosis, the pattern of human–computer interaction for enhanced clinical decision making, and the ethical principles and regulatory mechanism adhered to, and the practicing requirements of AI-CDSS will be crucial to accelerate the development of the industry.

(8) Off-target effects and their countermeasures

The off-target effects of novel gene editing technology refer to non-targeted site editing when using the CRISPR/Cas system. These non-target site editing events can be divided into sgRNA-dependent and -independent events. Previously, a variety of off-target detection methods have been developed that include off-target prediction software (e.g., CRISPR Design Tool, E-CRISP, and Cas-OFFinder), high-throughput genome-wide translocation sequencing, break labeling *in situ* and sequencing (BLESS), and genome-wide unbiased identification of DSBs enabled by sequencing (i.e., GUIDE-seq). However, the sensitivity and accuracy of these technologies cannot meet the needs of the growing field of gene editing. Currently, CRISPR/Cas possesses multiple functions, such as DNA double-strand breaks, DNA single-strand breaks, DNA targeting, RNA cutting, single-base editing, and prime editing, thus providing broad prospects for disease treatment. However, off-target effects have become a bottleneck for the clinical application of this technology. It is hoped that the safety evaluation of existing gene technologies and the development of new high-fidelity gene editing tools would make this technology suitable in a variety of situations. The problem of off-target effects seriously hinders the industrialization of gene editing technology. There is no medicine for diseases caused by gene mutations. The market for gene therapies that allow for correcting or compensating for mutated genes through gene editing is vast. The research and development pipelines of pharmaceutical giants cover several gene therapies, and original innovative drug R&D companies based on gene editing technology are rapidly emerging around the world. Currently, multiple CRISPR/Cas drugs are undergoing phase I/II clinical trials. Undoubtedly, there is a worldwide R&D competition. In the future, several gene therapies may enter the market one after another, and clinicians may be seeking a balance between the therapeutic effects and safety risks. In the long term, safety will be the goal pursued by this type of medicine, and in turn, achievement of this goal will promote the clinical application of gene editing technology. This reminds us that while promoting the development of new technologies, we should pay attention to reducing the off-target effects, establishing off-target effects quality control standards, and developing and optimizing a new generation of gene editing technologies to further promote the applications of gene editing technology.

(9) CAR-T treatment technology for solid tumors

CAR-T cell-based immunotherapy is an innovative approach to tumor treatment that has been demonstrated to potentially exhibit major histocompatibility complex-independent anti-tumor effects. These cells could directly recognize tumor cells by virtue of genetic modifications resulting in the expression of a chimeric antigen receptor (CAR), and they were activated to exhibit durable persistence *in vivo* through the action of a T cell activation endodomain with co-stimulatory signaling molecules. The screening of solid tumor target antigens, optimizing CAR affinity, hinge length, and flexibility and selection of stimulating molecules in the intracellular region can directly increase the homing, proliferation, and anti-tumor effects of CAR-T cells in patients with solid tumors, thus ensuring the long-term survival and anti-tumor ability of CAR-T cells *in vivo*. Additionally, specific issues related to the production of CAR-T cells, such as blood collection and transportation, preparation of viral vectors, and *in vitro* culture of autologous cells, are crucial for the treatment of tumors. The pharmaceutical evaluation of CAR-T cells should focus on the principle of "identification and control of drug safety and risks, taking into account the specificity of cell products." After two decades of preclinical research and clinical trials,

the safety and feasibility of CAR-T cell-based immunotherapy have both been confirmed, and unprecedented clinical results have been obtained for hematological malignancies such as B-cell lymphoma and leukemia. Additionally, CAR-T cell-based immunotherapy has been demonstrated to be safe and effective in the treatment of solid tumors, including non-small cell lung cancer, biliary tract cancer, pancreatic cancer, and liver cancer, suggesting a new treatment regimen for patients with solid tumors. On the basis of the broad application prospect of the CAR-T cell-based immunotherapy in tumor treatment, countries worldwide have attached great importance to research on CAR-T cells. A series of technology start-ups have been founded in recent years, and they have gradually achieved breakthroughs in improving the safety and efficacy of CAR-T cells with respect to the treatment of solid tumors. Based on this, the market for the technologies reached a certain scale and exhibited continuous high-speed growth. Selecting solid tumor target antigens such as neoantigens, choosing the appropriate conditioning regimens to disrupt the tumor microenvironment, improving homing ability and the ability to resist the tumor microenvironment for CAR T cells, and improving the clinical safety and efficacy are all vital for the treatment of solid tumors using CAR-T cells. Research and development in the field of CAR-T cell products is exhibiting an increasing trend, and this includes clinical trials on CAR-T cells that recognize different targets and improvements and optimization of these cells on the basis of these results. The continuous improvement of CAR-T cells will make them a powerful tool in the treatment of solid tumors, and it will significantly benefit the field in the future.

(10) Human microbiome diagnostic prevention and intervention

Human microbiome diagnostic prevention and intervention detects the second genome, i.e., the microbiome of humans to reflect the health status of various ecological niches and uses this information for the early detection of chronic diseases, the diagnosis of infectious diseases, and selection of biological interventions and treatments related to microorganisms in an effort to prevent the occurrence of diseases or to improve the health status. Through the use of amplicon sequencing, metagenomic or transcriptome sequencing, nucleic acid extraction, sequencing library construction, data analysis, and function prediction, human microbiome diagnosis prevention and intervention techniques can accurately analyze the human microbial flora spectrum to provide its function and expression, mine the key biomarker and species, outline the bacteria–host (people) relationship within the environment (ecological) complex, and provide accurate microbiota information for individual and population health and disease status. With the development of sequencing technology, human microbiome diagnostic prevention and intervention technology has been gradually applied in clinical practice at the scientific research level, including microbiome detection during early diagnostic screening of diseases, developing biotherapeutic drugs and agents targeting individual microbiomes, and improving individual health by the transplantation of intestinal flora. Additionally, metagenomics next-generation sequencing is widely used during diagnosis and treatment to assist in the precise treatment of clinically unidentified infectious diseases, such as central nervous system infections, respiratory tract infections, and blood flow infections. Advancements in the field of the human microbiome have broad prospects in the field of chronic disease prevention and control, personalized and precise diagnosis and treatment, and health management of microbial drugs and preparations, and these advancements are the strategic frontier of a new round of scientific and technological revolution. In recent years, a series of technology start-ups that include third-party medical detection, gene sequencing, molecular diagnosis, and microbial agents have gradually achieved technological breakthroughs in biological marker gene detection, microbiome diagnosis, and disease-specific target screening to launch new products based on the diagnosis of human microbiome prevention and intervention technology application products. This market formed at a certain scale, and the market scale has continuously experienced high-speed growth. The update of sequencing technology, the large-scale application of individual microbiome detection in popularization, the biological big data analysis ability, and the analysis of the association between the whole microbiome and the human genome will be the key for promoting human microbiome diagnosis prevention and intervention technology. The deep integration of human microbiome diagnosis with prevention and intervention technology and life and medicine, computer science, microbiology, and big data analysis will result in the development of new ideas for the diagnosis and management of chronic diseases, and this will also make microbiome technology a bridge between human health and microflora. The research achievements with respect to microflora, including early screening of non-

invasive colorectal cancer, individualized chronic disease and health management, probiotic intervention, and fecal bacteria transplantation, have been applied in the context of human health. In the context of the nternet era and with the progress in sequencing technology, the improvement in user education and acceptance, and the transformation of 2B (to business) to 2C (to consumer) business, the industrialization of human microorganisms will bring great benefits in the future to the medical field and the lives of people in general.

2.2 Interpretations for three key engineering development fronts

2.2.1 Development of vaccines and drugs for major infectious diseases

Since the Spanish influenza pandemic was recorded in 1918, severe acute respiratory syndrome (SARS), Ebola, hemorrhagic fever, Middle East respiratory syndrome (MERS), COVID-19, and other epidemics have emerged. The fight between human beings and infectious diseases has become increasingly fierce. By the 1940s, antibiotics were discovered to treat bacterial infections, and with the development of antibiotics, new drugs, vaccines, new diagnosis, and treatment technologies, an increasing number of infectious diseases could be prevented and treated. The development of vaccines has enhanced protection, especially in infants and young children, and has reduced their mortality. Similarly, vaccines have exerted an important protective effect on adults and have prevented the outbreak of pandemic diseases such as cholera and yellow fever. It has become clear that the quick development of vaccines and drugs for infectious diseases is a powerful weapon for human beings to fight against major infectious diseases.

Since 1970, more than 1500 new pathogens have been identified, and 70% of which have been shown to originate from animals, including the Ebola virus and the human immunodeficiency virus (HIV). As the COVID-19 epidemic continues to spread in 2020, the global need for drugs and vaccines to control and treat SARS-CoV-2 infections has never been more urgent. Some key technical challenges in the development of vaccines and drugs for major infectious diseases include means by which to rapidly detect and clarify unknown pathogens, methods to search for a safe and effective vaccine type for a certain disease, approaches to overcome the problem of genetic variation of pathogens, means by which to avoid and cope with pathogen drug resistance, and ways in which to achieve high efficiency in the monitoring and management of suspected infectious disease spread.

Currently, major international research has focused on a number of topics that include: (1) the completion of recognition of infectious disease monitoring systems, such as big data monitoring, rapid laboratory detection, gene sequencing, and others; and (2) the development of vaccines, which includes (i) establishment of a vaccine R&D and production platform for emerging infectious diseases that will allow researchers to produce a medicinal vaccine with a determined structure, antigenicity, purity, stability, and sterile need, (ii) development of multiple downstream and production processes to allow researchers to identify and save pathogens antigen protein structure characterizations, (iii) determining adjuvants and types of production, separation, and purification for vaccines, and (iv) establishing quality standards for vaccine evaluation and clinical research to allow researchers to perform relevant preclinical tests and clinical trials. The types of vaccines include inactivated vaccines, recombinant protein vaccines, virus vector vaccines, nucleic acid vaccines, and live attenuated vaccines. The research has also focused on 1) development of diagnostic tools such as nucleic acid diagnosis (e.g., polymerase chain reaction (PCR) targeted sequencing, portable rapid diagnostic sequencing, whole genome sequencing, RNA/cDNA sequencing, and epigenetic sequencing that can be used to analyze the genetic resistance of pathogens), imaging diagnosis, and direct observation of pathogens; and 2) development of therapeutic drugs, including blood products, immunotherapy, and drug therapy development.

By the end of 2018, a total of 77 preventive vaccines for 41 diseases were approved globally, and these covered approximately two-thirds of major infectious diseases. However, at the same time “vaccine hesitation” is likely to lead to a resurgence and increase in infectious diseases. Currently, there are still approximately 20 diseases such as malaria, hepatitis C, HIV, dengue fever, and MERS without effective vaccines. It is acknowledged that a 1 USD investment in vaccine research and development will result in savings between 2 USD and 27 USD in healthcare costs. The global vaccine market is expected to reach 44.8 billion USD in 2024, ultimately ranking 4th in all therapeutic areas.

Novel coronavirus infection caused large-scale infection and outbreak in the world. In the face of infectious diseases, China quickly responded and quickly established a research and development and production technology platform for such new infectious diseases. Achievements in epidemic prevention and control of coronavirus enabled China to reduce the social burden and avoid more economic losses to a certain extent. A large Chinese population brings huge demand for vaccines, and the development of effective vaccines will also reduce the burden of public health expenditure. In recent years, with the improvement of ability of individuals to pay and the enhancement of their awareness in preventing infectious diseases, the demand for vaccinations has been continuously increasing. The size of the Chinese vaccine market has increased from approximately 19.9 billion CNY in 2013 to 31.1 billion CNY in 2019, and the vaccine market is expected to develop rapidly.

The top five countries that published the most core patents are the United States, China, France, Japan, and the United Kingdom (Table 2.2.1). From the cooperation network among the major countries producing core patents (Figure 2.2.1), it can be observed that the United States closely cooperates with Switzerland, China, and Canada.

The top three institutions for core patent output were the U.S. Department of Health and Human Services, Novartis AG, and the University of Texas (Table 2.2.2). It can be observed from the cooperation network among the major institutions (Figure 2.2.2) that there is a partnership between the French National Centre for Scientific Research and the French National Institute of Health and Medical Research, and there is also a relationship between the U.S. Department of Health and Human Services and the University of California.

2.2.2 Development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases

Major emerging and re-emerging emergency infectious diseases refer to infectious diseases caused by new species or new pathogenic microorganisms and to those caused by reoccurring of ancient infectious diseases that seriously affect social stability and pose a major threat to human health. Laboratory testing for infectious diseases has passed through different stages that include the initial empirical diagnosis based on clinical symptoms, pathogen culture, serological testing, and modern comprehensive testing that is focused on the products of pathogens and host responses such as the combination of pathogen nucleic acid, antigen, and antibody tests. The development of laboratory technology provides indispensable technical means for epidemic monitoring, early diagnosis, and efficacy evaluation of infected patients.

Currently, the development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases depends upon solving key technical

Table 2.2.1 Countries with the greatest output of patents on “development of vaccines and drugs for major infectious diseases”

No.	Country	Published patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	USA	1 333	52.54%	20 022	66.42%	15.02
2	China	392	15.45%	1 183	3.92%	3.02
3	France	106	4.18%	895	2.97%	8.44
4	Japan	97	3.82%	877	2.91%	9.04
5	UK	96	3.78%	1 351	4.48%	14.07
6	Germany	91	3.59%	2 953	9.80%	32.45
7	South Korea	84	3.31%	98	0.33%	1.17
8	Switzerland	83	3.27%	1 370	4.54%	16.51
9	Canada	76	3%	1 160	3.85%	15.26
10	Netherlands	40	1.58%	658	2.18%	16.45

Figure 2.2.1 Collaboration network among major countries in the engineering development front of "development of vaccines and drugs for major infectious diseases"

Table 2.2.2 Institutions with the greatest output of patents on "development of vaccines and drugs for major infectious diseases"

No.	Institution	Published patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	U.S. Department of Health and Human Services	67	2.64%	736	2.44%	10.99
2	Novartis AG	39	1.54%	1 085	3.60%	27.82
3	University of Texas	37	1.46%	426	1.41%	11.51
4	French National Centre for Scientific Research	36	1.42%	235	0.78%	6.53
5	Gilead Sciences, Inc.	34	1.34%	976	3.24%	28.71
6	French National Institute of Health and Medical Research	33	1.30%	157	0.52%	4.76
7	Academy of Military Medical Sciences PLA	33	1.30%	41	0.14%	1.24
8	University of California	29	1.14%	769	2.55%	26.52
9	Harvard University	25	0.99%	627	2.08%	25.08
10	University of North Carolina	24	0.95%	148	0.49%	6.17

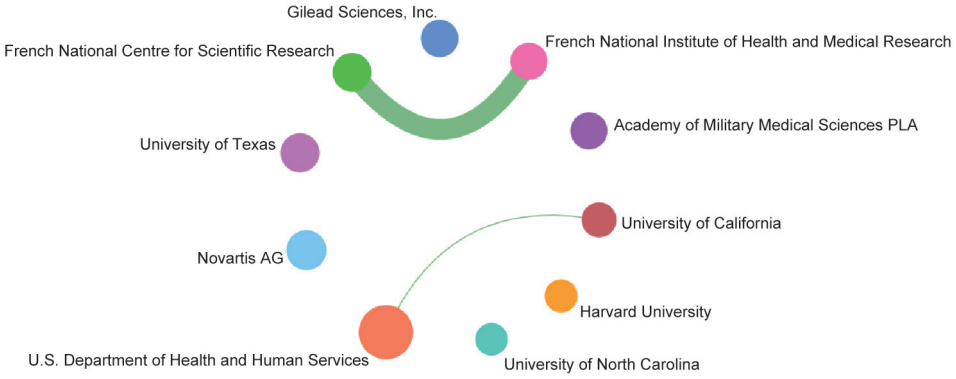

Figure 2.2.2 Collaboration network among major institutions in the engineering development front of "development of vaccines and drugs for major infectious diseases"

problems that include: 1) collecting pathogen strains from different regions to enrich the pathogen source library and gene information database to provide a prerequisite for the rapid identification and genetic variation monitoring of the pathogens that have caused emerging and re-emerging emergency infectious diseases; 2) developing key technical components of equipment to improve the testing speed, through-put, and sensitivity of equipment and to promote the functional integration, miniaturization, and portability of equipment to fulfill the different practical application needs of centralized detection and individual detection in different scenarios, and 3) performing innovative research on the key materials of diagnostic reagents and the principles of testing methods to improve the testing sensitivity and specificity. The global demand for diagnostic reagents and equipment is growing continuously. The global market size for infectious disease *in vitro* diagnostic (IVD) reagents and equipment was valued 16.3 billion USD in 2019 with a compound annual growth rate of approximately 7.4% from 2020 to 2027, and it is expected to reach 23.17 billion USD in 2027. This is closely related to favorable government initiatives and to an increase in research and development funds.

The current hotspots in the clinical application of diagnostic reagents and equipment for infectious diseases including: 1) Real-time PCR, a classic pathogen nucleic acid testing technology, has been developed to further improve the speed, sensitivity, throughput, and automation under the premise of ensuring the accuracy of the results. 2) Isothermal nucleic acid amplification technology was also able to achieve rapid amplification of target nucleic acids at constant temperature by incorporating the use of new nucleases. Currently, isothermal amplification technologies primarily include loop-mediated isothermal amplification, recombinase polymerase amplification, nucleic acid dependent amplification detection, and transcription-mediated amplification. 3) Hybridization and mass spectrometry analysis are additional technologies that must be discussed. Molecular nucleic acid hybridization is a technique used to analyze nucleic acids qualitatively and quantitatively based on nucleic acid denaturation and renaturation. Such technology attaches target DNA fragments to a solid matrix such as a membrane, glass, latex particles, or nanoparticles, and it can then be used for multiple pathogens testing according to hybridization and fluorescent labeling. 4) High-throughput sequencing is primarily used in the diagnosis of infections that are acute, complicated, and in the identification of difficult-to-cultivate or new pathogens. Additionally, it also plays an important role in tracing the source of infectious diseases and in epidemic monitoring and control. 5) Immunologic tests primarily include antigen testing against pathogens and host humoral and cellular immune response tests. Antigen testing employs specific antibodies to detect antigens of a pathogen to determine the existence of an infection caused by a specific pathogen. Antibodies conversing from negative to positive or a significant increase in antibody titer can be used to make laboratory diagnoses for pathogens as well as to evaluate the severity and population prevalence of the pathogenic infection during the outbreak of infectious diseases.

China is a large country with a large population. Due to the economic integration and globalization, the changes in living habits, etc., China has experienced outbreaks of several emerging and re-emerging emergency infectious diseases since the SARS outbreak in 2003. In the course of fighting against the COVID-19 epidemic, with the active support of the government and the sufficient investment of scientific research funds, increasing IVD reagent and device manufacturers and scientific research institutions have joined into the research and development of diagnostic reagents and equipment. They have developed dozens of nucleic acid and antibody testing reagents, as well as rapid PCR amplification devices, microfluidic nucleic acid microarray platforms, portable molecular nucleic acid detection workstations, and other new equipment. Such diagnostic reagents and equipment played a critical role in pathogen identification, laboratory diagnosis, efficacy assessment, early warning, and monitoring of the epidemic.

As shown in Table 2.2.3, the United States, China, South Korea, Japan, and Germany are ranked as the top five countries in terms of the number of active patents. The patents output by Chinese researchers account for 28.74% of the global total, ranking second only to the United States. As shown in the collaboration network of the top 10 patent-producing countries (Figure 2.2.3), the United States has close collaborations with Germany, Switzerland, Canada, and China in this field.

The top three institutions in terms of patent output in this front are the U.S. Department of Health and Human Services, the Academy of Military Medical Sciences PLA (China), and Curetis GmbH (Germany) (Table 2.2.4). Additionally, the collaboration network of the top 10 patent-producing institutions shows cooperation between Curetis GmbH and Ares Genetics GmbH (Germany) and between the French National Centre for Scientific Research and the Institut Pasteur (Figure 2.2.4).

2.2.3 Human organoids-on-a-chip technology

Human organoids-on-a-chip technology has been highly valued and regarded as a catalyst for the development of translational medicine due to its feasibility with respect to multi-organ integration and high bio-functional simulation. The fact that organoids-on-a-chip can serve as substitutes for animal models has tremendous strategic significance, and this technology has therefore been important for the development of new drug evaluation systems.

Several vital scientific issues underlying human organoids-on-a-chip primarily include the structural design of chips, the expansion of the cell or tissue sources, appropriate substitutes for the extracellular matrix, the development of cell substrates, the exploration of the co-culture system, the combination of multi-organoids and their bio-functions, the regulation and control of the inner microenvironment, and

Table 2.2.3 Countries with the greatest output of core patents on “development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases”

No.	Country	Published Patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	USA	320	38.00%	5 706	73.37%	17.83
2	China	242	28.74%	560	7.20%	2.31
3	South Korea	68	8.08%	32	0.41%	0.47
4	Japan	41	4.87%	157	2.02%	3.83
5	Germany	37	4.39%	525	6.75%	14.19
6	Switzerland	20	2.38%	269	3.46%	13.45
7	France	20	2.38%	153	1.97%	7.65
8	UK	18	2.14%	172	2.21%	9.56
9	Canada	16	1.90%	256	3.29%	16.00
10	India	13	1.54%	48	0.62%	3.69

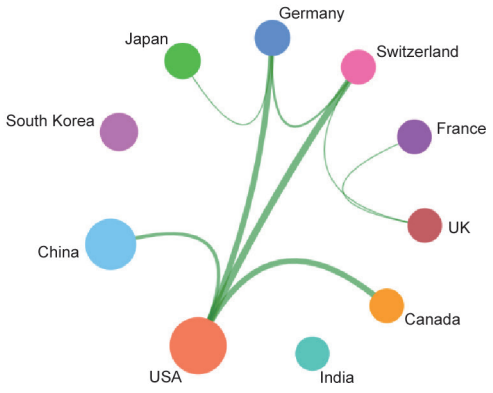

Figure 2.2.3 Collaboration network among major countries in the engineering development front of “development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases”

Table 2.2.4 Institutions with the greatest output of core patents on "development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases"

No.	Institution	Published Patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	U.S. Department of Health and Human Services	19	2.26%	142	1.83%	7.47
2	Academy of Military Medical Sciences PLA	14	1.66%	13	0.17%	0.93
3	Curetis GmbH	14	1.66%	12	0.15%	0.86
4	University of Texas	12	1.43%	111	1.43%	9.25
5	Ares Genetics GmbH	9	1.07%	12	0.15%	1.33
6	Harvard College	8	0.95%	504	6.48%	63.00
7	Institut Pasteur	8	0.95%	88	1.13%	11.00
8	French National Centre for Scientific Research	8	0.95%	45	0.58%	5.63
9	Coyote Bioscience Company	8	0.95%	3	0.04%	0.38
10	Korea Center for Disease Control and Prevention	8	0.95%	1	0.01%	0.13

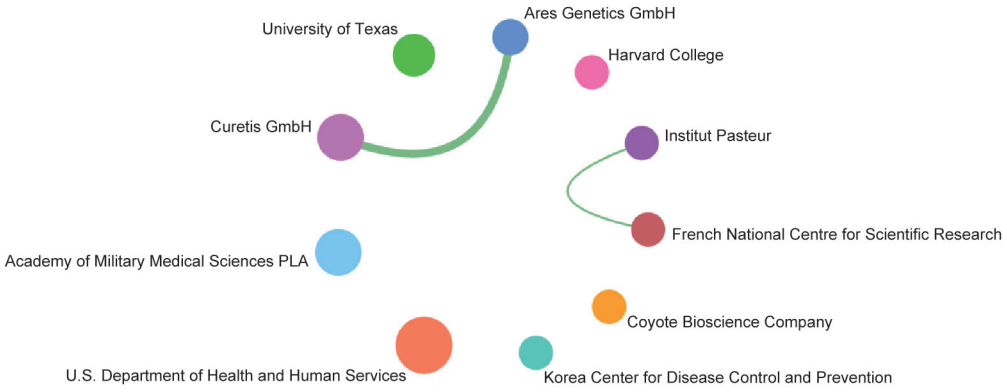

Figure 2.2.4 Collaboration network among major institutions in the engineering development front of "development of diagnostic reagents and equipment for major emerging and re-emerging emergency infectious diseases"

the integration of the detection and sensing units. The current hot topics have focused on the following seven aspects.

(1) Intelligent biomaterials. Studies are focused on the development of controllable functionalized biomaterials, such as patterned surfaces for cellular orientation induction, selective-permeable membranes for liquid ion exchange, biomimetic vessels, and 3D bio-scaffolds to improve the bio-functions by adjusting the composition of materials, the structure of substrates, and other parameters.

(2) Interaction between substrates and cultured cell clusters. The research aims to determine the impact of material properties, such as rigidity and viscoelasticity on cell adhesion, migration, and proliferation, as well as the impact of material structural properties, such as microstructures, nanopatterns, and dynamic variations on cell growth, migration, and stem cell differentiation. The further stages aim to develop the most suitable biomaterials that match each organoid for regenerating organ capabilities and to construct organ-chips that include heart-on-chips, liver-on-chips, lung-on-chips, kidney-on-chips, bladder-on-chips, intestine-on-chips, pancreas islet-on-chips, amnion cavity-on-chips, and skin-on-chips.

(3) Construction of cell co-culture systems. Multi-structured organoids-on-a-chip, such as chips with multi-layer structures, tube-shape networks, loop structures, or multi-regions, are

required to develop cell co-culture systems. Studies on the interaction of each type of cells and tissues are combined with microfluidic chips for simulating *in vivo* tissue structure and fluid circulation. By controlling signal interactions between cells and between cells and scaffolds, these devices could achieve organ functions and cooperation *in vitro*. The research aims to construct organ co-culture systems combining heart, liver, lung, and kidney, and vessel-related co-culture systems with cancer cells, vascular endothelial cells, and fibroblasts.

(4) Organoid real-time monitoring. The research aims to develop biomaterials with signal transformation capability to act as integrated sensing and imaging units in organoids-on-chips. The further stages aim to detect and analyze real-time cell state inside chips based on electric or optical signals of sensing elements, which are corresponding signal-transforming units of electric, electrochemical and optical materials designed for different physiological characteristics of various organ cells. Utilizing multi-structure chips, the driving systems and auxiliary devices are connected onto the chips to attain liquid cycling inside the chip and allow for dynamic cell monitoring.

(5) Internal micro-environmental regulation. This involves the use of organoids-on-chips with oxygen concentration controllability to simulate the oxygen environment in different organs *in vivo*. The differences in morphology and function of cells from the placenta, lung, heart, and other organs could be observed and studied under different oxygen conditions. Integrating functional biomaterials, sensors, and imaging units within the microfluidic chips can allow for the real-time monitoring of the biomarkers and metabolites of cells during each biochemical stage, and this technology will allow researchers to determine the dynamic distribution of pH, oxyhemoglobin saturation, and other factors inside the chip.

(6) Connection and cooperation of multiple organoids-on-chips. This requires the formulation of strategies for culturing different cells with different growth conditions on the same microfluidic chip. The research aims to construct microfluidic chips with multi-cavity or multi-layer structures, design microchannels to simulate circulatory system and explore integration ways of different organoids-on-chips. This will allow researchers to investigate the functional integration of multi-organoids-on-chips, the interaction among different cells, simulate the signal conduction in organoids, and integrate and cooperate organ functions within a single chip.

(7) Drug screening, toxicity classification, and mold establishement. This would require combining analysis techniques and real-time monitoring techniques for organ feature extraction to investigate cellular bio-information and resistance law under drug condition and further construct drug evaluation system based on human organoids-on-chips. Based on the typical cellular physiological reactions to the presence of compounds, this approach would enable toxicity screening and poison classification via electrochemical, optical, bioinformatics, and other analytical methods. Utilizing cells with differentiation potential, this technology could be used to simulate organ formation, growth, and maturity, and thus construct original organoid developmental models. The pathological organ model and drug evaluation model could be developed by developing channel networks and fluid circulation, and further investigating the reaction and interaction between organoid cells and additives such as nanoparticles, surfactants, and pharmaceuticals in circulating fluid chips.

Although research focused on organoids-on-a-chip is still in its initial stages, it has been highly valued due to its vast potential and development prospects. In respect to the status, western research institutes and biotechnology companies are promoting the development of related technologies, and they have already dominated some essential technological patents. As a trend of constructing new drug evaluation systems, organoids-on-a-chip possesses great strategic significance for supporting national innovative drug research and translational medical development. Over the recent years, the share of international patents for human organoids-on-a-chip from China has been gradually rising, which reflects the progress in related research. Whereas, it still exist challenges to meet the requirements, such as human physiological chip-systems construction, multi-organ functional association and synergy, chips standardization and sensing-detection integration.

Core patents have been applied for human organoids-on-a-chip. The United States, China, Germany, the Netherlands, and Japan are ranked as the top five countries with the most patents (Table 2.2.5). As shown in the cooperation network of patent-producing countries (Figure 2.2.5), China, the United States, and Singapore cooperate most closely.

The top three institutions with the most inventors of the core patents in force are Harvard University, the Graduate School at Shenzhen of Tsinghua University, and Emulate Inc. (Table 2.2.6). Additionally, the collaboration network among international institutions reveals cooperation between Harvard University and Vanderbilt University and among TissUse GmbH, Tesyus Inc., and University of Berlin (Figure 2.2.6).

Table 2.2.5 Countries with the greatest output of core patents on "human organoids-on-a-chip technology"

No.	Country	Published patents	Percentage of published patents	Citations	Percentage of citations	Citations per patent
1	USA	42	38.89%	343	74.08%	8.17
2	China	40	37.04%	35	7.56%	0.88
3	Germany	6	5.56%	75	16.20%	12.50
4	Netherlands	6	5.56%	4	0.86%	0.67
5	Japan	5	4.63%	5	1.08%	1.00
6	South Korea	4	3.70%	0	0.00%	0.00
7	UK	2	1.85%	0	0.00%	0.00
8	Singapore	2	1.85%	0	0.00%	0.00
9	Russia	1	0.93%	1	0.22%	1.00
10	Switzerland	1	0.93%	0	0.00%	0.00

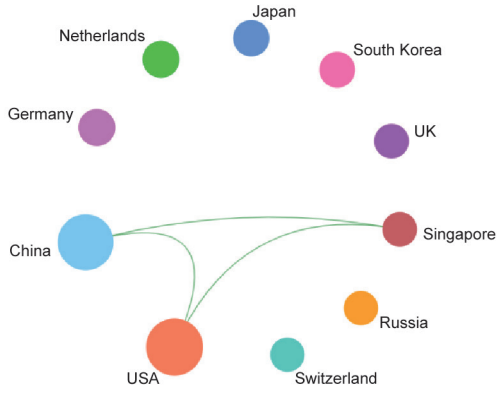

Figure 2.2.5 Collaboration network among major countries in the engineering development front of "human organoids-on-a-chip technology"

Table 2.2.6 Institutions with the greatest output of core patents on "human organoids-on-a-chip technology"

No.	Institution	Published patents	Percentage of published patents	Citations	Percentage of citations	Citation per patent
1	Harvard University	15	13.89%	279	60.26%	18.60
2	Graduate School at Shenzhen, Tsinghua University	5	4.63%	20	4.32%	4.00
3	Emulate Inc.	5	4.63%	17	3.67%	3.40
4	TissUse GmbH	4	3.70%	73	15.77%	18.25
5	Massachusetts Institute of Technology	4	3.70%	0	0.00%	0.00
6	Dalian Institute of Chemical Physics, Chinese Academy of Sciences	3	2.78%	2	0.43%	0.67
7	BGI Shenzhen	3	2.78%	0	0.00%	0.00
8	Vanderbilt University	2	1.85%	110	23.76%	55.00
9	Tesyus Inc.	2	1.85%	58	12.53%	29.00
10	University of Berlin	2	1.85%	9	1.94%	4.50

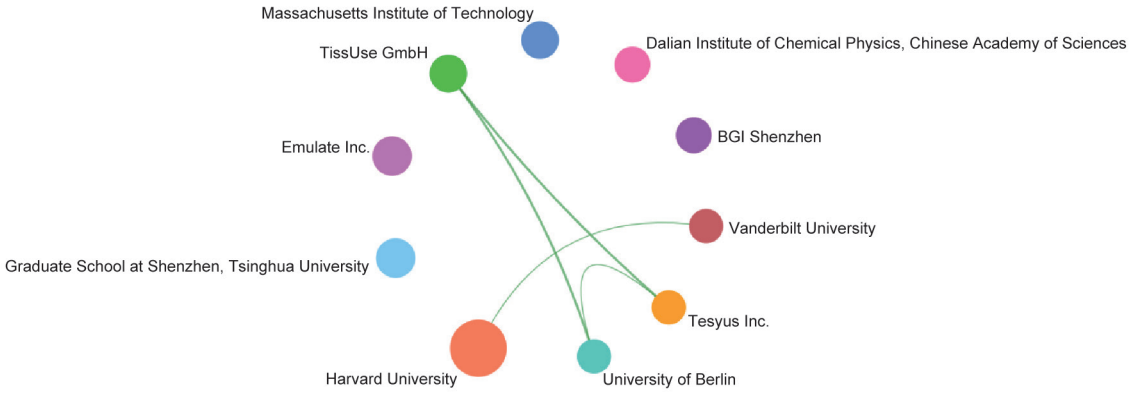

Figure 2.2.6 Collaboration network among major institutions in the engineering development front of "human organoids-on-a-chip technology"

Participants of the Field Group

Leaders

CHEN Saijuan, ZHANG Boli

Academicians

GU Xiaosong, HUANG Luqi, LI Zhaoshen, LI Xiaokun, SHEN Hongbing, TIAN Wei, ZHANG Zhiyuan, ZHANG Xue

Other Experts

SHI Jian , ZOU Wenbin, TAO Fangbiao, GAO Pei, WU Shaowei, ZHOU Zhou, CHEN Rui, QU Weidong, KAN Haidong, YANG Yanjie, HE Jia, LIAO Xiaoping, CAO Jia, XIA Ningshao, XI Bo, ZHANG Ben, ZHANG Yonghong, TANG Naijun, SHAO Yiming, LI Tiantian, PI Jingbo, LU Xiangfeng, SHU Yuelong, XIA Min, JING Guangfu, GU Aihua, ZHAO Liping

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, ZHANG Yang

Report Writers

Engineering Research Front

SHEN Hongbing, SHU Yuelong, SHI Xiaoming, YANG Weizhong, FENG Luzhao, ZHANG Ting, QIN Chengfeng, LI Lanjuan, LYU Longxian, HAN Zhongchao, FU Xiaobing, TIAN Wei, HAN Xiaoguang, FENG Jianfeng, XIE Xiaohua, CHEN Houzao, XU Xiping, HUANG Luqi, ZHANG Xue, ZHENG Tongsen

Engineering Development Front

ZHANG Yuntao, WANG Xuewei, SHANG Hong, ZHONG Ping, HAN Xiaoxu, CHEN Yu, LI Jinming, XIA Ningshao, DENG Zhongping, WANG Youchun, PAN Boshen, CHEN Wenxiang, ZHAO Yuanjing, YANG Caiguang, XU Ruihua, ZHAO Hongyun, LI Chengquan, LI Lanjuan, HE Qianfeng, ZHU Yelin, LI Yingying, YANG Hui, ZHANG Hainan, HUO Xiaona, ZUO Erwei, HAN Weidong, XU Jianguo, YANG Jing, PU Ji