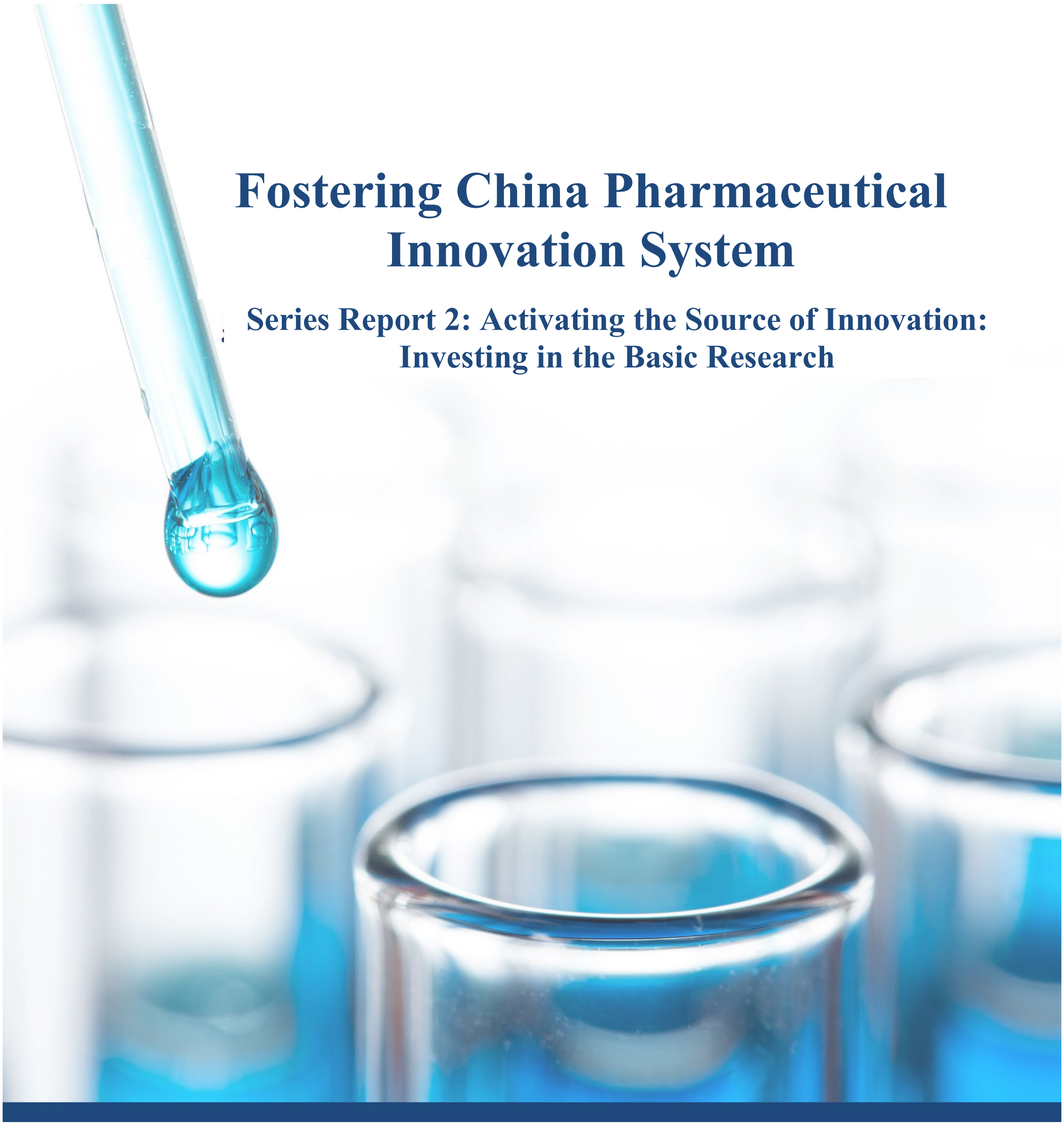
Fostering China Pharmaceutical Innovation System

Series Report 2: Activating the Source of Innovation: Investing in the Basic Research



China Pharmaceutical Innovation and Research Development Association (PhIRDA)

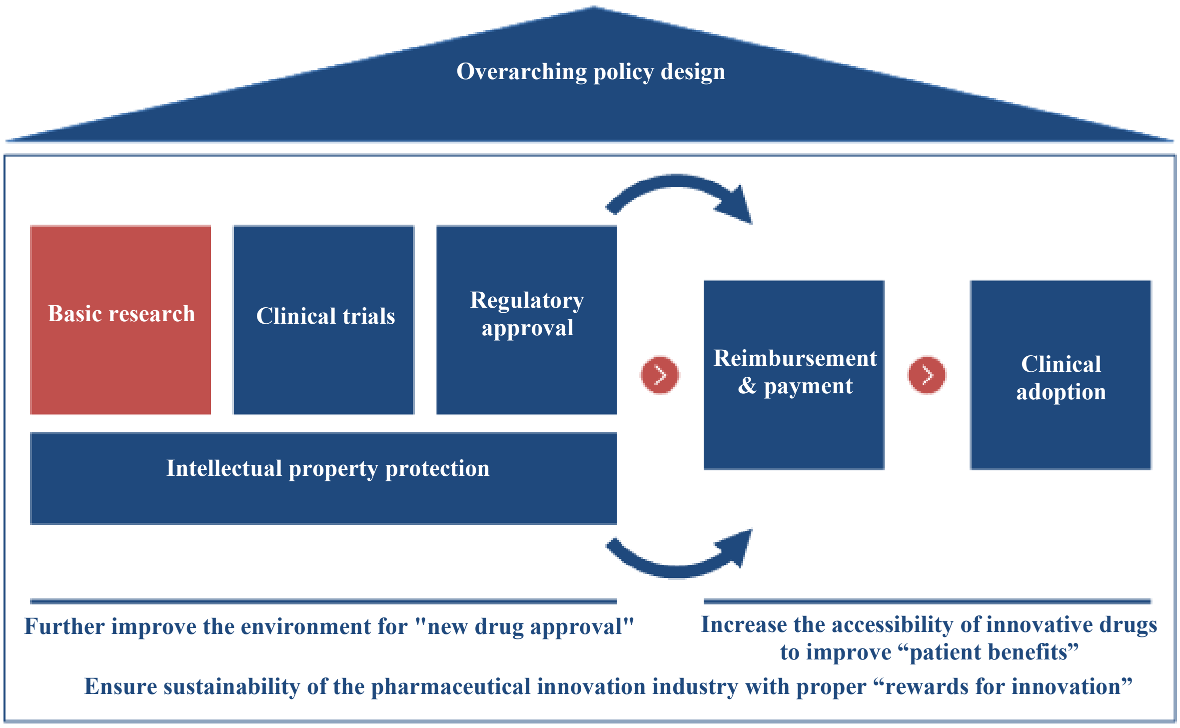
R&D-based Pharmaceutical Association Committee (RDPAC)

June, 2021

Preface

The *Fostering China Pharmaceutical Innovation System* is a series of reports, of which *Report 1: 2015-2020 Review and Future Outlook* outlines the framework of an ecosystem for pharmaceutical innovation from 2021 to 2025, and *Report 2: Activating the Source of Innovation: Investing in the Basic Research*" focuses on the sources of sustainable development of pharmaceutical innovation ecosystem. "Basic research", as the initial step prior to "clinical research" and "regulatory review and approval", mainly includes the research on disease mechanisms, target identification and validation, drug screening and optimization. This report reviews the significant progress made in China's basic pharmaceutical research in the past five years, assesses comprehensively global competitiveness, and summarizes major challenges faced in various elements of basic research. Based on these, it makes recommendations on how to advance basic research in China in the next five to ten years, drawing on experiences of leading biopharmaceutical countries around the world.

Figure 1: China pharmaceutical innovation ecosystem (2021-2025): basic research is the source of innovation



The irreplaceable significance and role of basic research is to provide a source of breakthrough and original innovation for China's pharmaceutical innovation ecosystem. Firstly, basic research opens up and challenges unknown fields through pioneering scientific discoveries and breaks the boundaries of human cognition of life and disease mechanisms; secondly, basic research enables the iterative updates of tool performance through disruptive technological inventions that enrich and enhance the human response to disease threats; and thirdly, basic research is the source of innovation at the forefront of the pharmaceutical R&D value chain that realizes the industrial translation of scientific and technological achievements and provides an innovation engine for pharmaceutical R&D via the translational research such as target identification and validation, drug screening and optimization.

In the past five years, under the guidance of the implementation of innovation-driven strategies, China has made remarkable achievements in basic biopharmaceutical research by relying on increasing funding and continuously optimized regulatory mechanisms: reinforced strength of research institutions, expanded talent team, accelerated translation of scientific and technological achievements, and fast-rising papers and patents. However, the basic research has yet to play its role in full as a source of innovation in China's ecosystem for pharmaceutical innovation today, leading to lagging behind the world's leading level. On the one hand, the contribution of pioneering scientific discoveries and disruptive technical inventions is still low, and follow-up research is predominant in the hot research fronts; on the other hand, the system and capacity for the translation of basic research into the industry still need to be developed, and the generation and application of local intellectual property are insufficient.

Strengthening basic research to promote pharmaceutical R&D requires the support of key elements such as funding, core resources, innovators, and talent structure. At present, the four key elements are all faced with certain challenges: the funding obtained by the source of innovation is relatively insufficient, and the government investment needs to be further coordinated and efficient; there is still a risk of "being hit in the throat" in the production and supply of core resources like high-end laboratory equipment, reagent materials and laboratory animals needed for the biomedical information and data storage and basic research. The scientific research evaluation mechanism pose constraints on the innovation vitality, and it is relatively limited that the cross-border cooperation among various innovators from the industry, academia, medicine and scientific research; the global competition for talents is unprecedentedly fierce, there is still room for improvement in the talent evaluation mechanism and a great gap between cross-disciplinary and inter-disciplinary talents, which can hardly meet the demand of the innovation chain.

Recently, General Secretary Xi Jinping pointed out that sci-tech self-reliance and self-strengthening should always be considered a strategic support for national development, called for efforts to tackle problems in science and technology that are original and lead the way, and resolutely achieve breakthroughs in core technologies in key fields at the meeting conflating the general assemblies of the members of the Chinese Academy of Sciences and the Chinese Academy of Engineering, and the national congress of the China Association for Science and Technology. Looking into the future, the continuous promotion of basic research in China needs to be centered on improving the talent system, with a multi-pronged approach on strategic direction, funding and innovators: to lay out the direction of national strategic research towards the world frontiers; to improve the efficiency of funding management and use in key parts; to explore the upgrading of the mode regarding innovators focusing on innovation chain; and to optimize the talent training and evaluation mechanisms in response to future needs. Doing so is expected to consolidate the foundation of basic research and guard the source of scientific and technological innovation.

The preparation of the report gained strong support from various experts. Special thanks have been given to Ruiping Xiao, College of Future Technology, Peking University & Co-founder of Hope Medicine, Jia Li, Director of Shanghai Institute of Materia Medica, Chinese Academy of Science, and Ao Zhang, Dean of School of Pharmacy, SJTU for their in-depth insights and suggestions, and sincere appreciation is hereby extended to experts for their guidance.

China Pharmaceutical Innovation and Research Development Association **(PhIRDA)**

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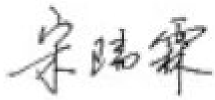

R&D-based Pharmaceutical Association Committee (RDPAC)

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Chapter 1

Progress in Basic Pharmaceutical Research in China and Comparison with International Levels

Great progress has been made in basic biopharmaceutical research in China in the past five years

In the past five years, China's basic biopharmaceutical research has embarked on a fast track under the guidance of the national innovation-driven development strategies and a series of overarching plans for scientific and technological innovation. Thanks to the continuous improvement in key elements including funding, innovators, talent strategies and institutional environment, the solid foundation has been laid for significant progress that has been made in basic biopharmaceutical research.

1. Implement innovation-driven strategy and strengthen overarching planning for scientific research

Implement innovation-driven strategy: in order to fully implement the innovation-driven development strategy unveiled at the 18th National Congress of the Communist Party of China (CPC), the Central Committee of CPC and the State Council issued the *Outline of the National Innovation-driven Development Strategy* in May 2016, designed to implement the national major development strategy based on the overall situation, oriented to the world, focusing on critical domains and driving the whole. It also sets the tone for China's biopharmaceutical industry to enter the fast track to innovation.

Strengthen overarching planning for scientific research: in order to undertake the innovation-driven development strategy, the State Council issued the *Plan for National Scientific and Technological Innovation in the "13th Five-year Plan"* in August 2016, which for the first time includes "scientific and technological innovation" as a whole for overarching planning. The *Special Plan for National Basic Research in the "13th Five-Year Plan"* and the *Special Plan for Biotechnology and Innovation in the "13th Five-Year Plan"* were subsequently introduced in May 2017 to accelerate the development of basic research and biotechnology in the scientific and technological innovation system. The above plans have been dissected from outline to planning, so as to refine the implementation plans of strategy.

Strengthen national strategic priorities: as we enter the "14th Five-Year Plan", China will embark on a new journey towards building a modern socialist country in all respects as the second centenary goal. China's guiding principles for the development of science and technology have evolved from 2016 to 2020 to cover four key elements, now emphasizing "people's lives and health" together with "the frontiers of world science and technology", "the main economic battlefield" and "the major needs by the country". Against this background, *the Outline of "14th Five-year Plan" and the Vision for 2035* was released in March 2021, indicating the priorities and development goals for strengthening the country's strategic science and technology forces, and that adhering to the "innovation-driven development" will become China's core strategy in the next five years and mid-long term. It is also clearly stated that the proportion of funding for basic research to R&D investment will be increased to more than 8%.

2. Optimize system for scientific and technological plan and promote Major New Drug R&D Project

Optimize system for scientific and technological plan: important progress has been achieved in the reform of the management of scientific and technological plans (projects and funds) financed by the Central Government implemented since early 2015. The state optimizes the system and layout of the original scientific and technological plans (projects and funds) with the outset in strengthening the overarching design and removing barriers between regions and departments to solve problems such as duplication, fragmentation, closure and inefficiency that existed at that time. The new system for scientific and technological plans was preliminarily formed in 2017 that established an open and unified national scientific and technological management platform, and integrated into five new categories of scientific and technological plans (projects and funds) including National Natural Science Foundation of China(NSFC), National Science and Technology Major Project, National Key R&D Program of China, Technology Innovation Guidance Project, Base and Talent Project, so as to improve the allocation efficiency of scientific and technological resources.

Promote Major New Drug R&D Project: as a critical part of China's mid- and long-term scientific and technological development plan, the "Major New Drug R&D Project" was launched in 2008 and ended in 2020. The central government has invested a total of 23.3 billion yuan, provided support for more than 3,000 topics, and achieved remarkable results in pharmaceutical innovations targeting 10 major diseases. Since the implementation of the Major New Drug R&D Project, China has initially established a drug innovation technology system, including national-level comprehensive technology platform mainly in scientific research institutes and colleges & universities, drug innovation technology platform for enterprises, and unit platform that provides evaluation and support for new drug R&D.

Step up efforts to ensure funding: the whole society makes sustained efforts to support the basic research. The total R&D investment in China reached CNY 2,442.6 billion in 2020, accounting for about 2.4% of GDP. Of these, the basic research investment was 150.4 billion yuan, and the proportion of basic research investment to the total R&D investment increased from 5.1% in 2015 to 6.1% in 2020; and the five-year average compound annual growth rate (CAGR) was about 16.0%[1], which is higher than the growth rate of total R&D investment.

3. Reinforce the strength of research institutions and explore new R&D models

Reinforce the strength of research institutions: China's research institutions have risen in the international rankings, and there are more Chinese institutions that rank among the world's leading scientific research institutions in life sciences. The number of China's research institutions is on the rise among the world's leading institutions in life sciences in the Nature Index tables. Only four Chinese institutions were listed in the top 100 institutions in 2015, but the number reached 9 in 2019. Chinese Academy of Sciences (CAS), Peking University, Tsinghua University and Fudan University, which gained the position in the 2015 Annual Tables, have greatly risen up the ranks.

Figure 2: Increasing number of Chinese top-notch research institutions in life sciences in recent years

Number of Chinese institutions in the top 100 global institutions in life sciences in the Nature Index[1]

Chinese institutions in 2015 Annual Tables		Chinese institutions in 2019 Annual Tables	
Ranking	**Institution**	**Ranking**	**Institution**

[1] Statistical Bulletin on National Funding Investment in Science and Technology

8	Chinese Academy of Sciences	5	Chinese Academy of Sciences
67	Peking University	31	Peking University
74	Tsinghua University	52	Tsinghua University
99	Fudan University	54	Zhejiang University
		60	University of Science and Technology of China
		65	Fudan University
		68	Shanghai Jiao Tong University
		76	Sun Yat-sen University
		92	China People's Liberation Army National Defense University

1. Reflects high-quality output based on publications in 82 high-quality natural science journals
Source: Nature Index

Continuously promote national academic institutes: China has built a system for national natural science and medical research with a relatively complete disciplinary layout. As China's top academic institute for natural science research, **CAS** is the highest advisory body for science and technology, and a comprehensive research and development center for natural science and technology. Its basic research system is composed of 115 research units, with research fields covering mathematics, physics, chemistry, biology, engineering, environment, information and many other basic and applied disciplines. Relying on research units, CAS also has multiple innovation units in forms of national and academic-level key laboratories, research centers, major scientific and technological infrastructure and sharing service platforms for national scientific and technological resources. The innovation unit plays a leading role in undertaking the national strategic directions and leading scientific progress by focusing on basic, cutting-edge and interdisciplinary research directions and providing basic scientific and technological support services. With 23 research institutes, 6 hospitals, 7 colleges and 56 innovation units, the **Chinese Academy of Medical Sciences (CAMS)** is a national medical science center and a comprehensive research institute in medical science integrating healthcare, education, research, prevention and production. The 23 research institutes are the primary players in medical scientific research in CAMS, covering various disciplinary directions like clinical medicine, basic medicine, pharmacy and biomedical engineering, and multiple organs and disease areas such as cardiovascular, dermatology, hematology, oncology and neuroscience. The innovation units with nominal funding by CAMA are research players established by external research institutes to complement and extend the internal research directions through complementary resources between CAMS and academic collaborators.

Explore new R&D models: domestic research institutes are also actively exploring innovative R&D models to break through simple basic research functions, combine research with production to promote the migration of basic research findings to the application side, better realize the role of innovation source, and further create commercial and social values. For example, taking the industry as the orientation, Shenzhen Institute of Advanced Technology, CAS concentrates on the integration of intelligent technology and biotechnology. It has built a micro-innovation R&D ecosystem integrating research, education, industry and capital through collaboration with research institutes and local governments, and signed more than 700 contracts with enterprises with respect to industrial entrusted development and the translation of basic research achievements so far. Besides, 1,186 enterprises have been incubated cumulatively.

Another example is Shanghai Institute of Materia Medica (SIMM), CAS that has been exploring measures on mechanisms and systems reform to promote the translation of scientific and technological achievements since 2015, which vigorously advances the implementation and improvement of the achievement translation system, and achieves substantial acceleration in the translation of achievements. After the promulgation of the system for the translation of basic research outcome, SIMM has also formulated the measures on self-employment and part-time entrepreneurship for scientific researchers, and funded 50 million yuan per year to support earlier drug research and development. All of these actions accelerate the efficiency of translating scientific and technological achievements from various aspects like institutional guarantee, standard processes and financial support. SIMM has translated 50 scientific and technological outcomes since 2015, and the value of contracts on translation of scientific and technological outcomes amounted to 1.717 billion yuan in 2019, ranking the first in the China's scientific research institutes and colleges and universities.

4. Guide the direction of talent development and enrich the team of leading talents

Guide the direction of talent development: China has been making sustainable efforts to guide the development of biomedical talents from a perspective of overarching design. The effective measures and suggestions have been proposed in the *National Medium and Long-term Biotechnology Talents Development Plan (2010-2020)* introduced in 2011 and *Plan for Development of National Scientific and Technological Talents in the "13th Five-Year Plan"* issued in 2017 to promote innovation and entrepreneurship of biotechnology talents, encourage cross-field and cross-region mobility, support fiscal taxation and financial innovation and international cooperation, and strengthen the introduction of high-level overseas talents. Under the direction of the national overarching design, the local governments have issued relevant policies to accelerate the construction of local biopharmaceutical talent teams both in introduction and cultivation.

Enrich the team of leading talents: in the past ten years, China has made the groundbreaking achievements in the top international prizes in the biopharmaceutical science (Tu Youyou, winner the 2011 Lasker Award and the 2015 Nobel Prize). As the backbone of basic biopharmaceutical research, the number of high-level talents has increased and the reserve of outstanding young talents has been gradually strengthened. The number of high-level talents whose papers have been cited in the world's top 1% by citations in biopharmaceutical field increased from 6 in 2015 to 22 in 2020; in terms of outstanding young talents, by 2020, a total of 15 Chinese scientists in the biopharmaceutical field have won world-renowned Young Scientist Awards, accounting for 15.6% of the total number of winners worldwide[2].

5. Optimize regulatory and institutional environment to encourage the translation of scientific and technological achievements

[2] Including Science & SciLifeLab Prize for Young Scientists and World Economic Forum Young Scientists

Encourage the translation of scientific and technological achievements: a series of laws/regulations were successively released to encourage translation of scientific and technological achievements. Firstly, the *Law on Promoting the Translation of Scientific and Technological Achievements* was revised; secondly, *Provisions on Implementing the Law on Promoting the Translation of Scientific and Technological Achievements* were introduced to clarify supporting rules; thirdly, specific tasks were deployed by adopting the *Action Plan for Promoting the Transfer and Translation of Scientific and Technological Achievements*. In accordance with these laws/regulations introduced intensively in 2015 and 2016, the relationship among the government, research institutions and researchers were clarified, and the right of usage, disposal and earnings from scientific and technological achievements were delegated to scientific research institutions. In February 2020, the Ministry of Education, China National Intellectual Property Administration and Ministry of Science and Technology introduced the *Opinions on Improving Patent Quality and Promoting Translation and Utilization in Colleges and Universities,* which further offers guidance on implementation to comprehensively improve patent quality in colleges and universities, strengthen the creation, utilization and management of high-value patents, and better play a key role of colleges and universities in serving economic and social development. According to *2020 Annual Report on Translation of Scientific and Technological Achievements in China (Colleges and Universities and Scientific Research Institutes),* in 2019, 15,035 contracts were signed on the translation of scientific and technological achievements by transfer, licensing and evaluation investment in 3,450 public colleges and universities and scientific research institutes nationwide, representing an increase of 32.3% compared with the previous year; 10,770 R&D institutes, transfer institutions and translation service platforms were established with enterprises, registering an increase of 27.2% over the previous year.

6. Boost output of high-quality papers and increase in number of patents

Boost output of high-quality papers: the number of papers published in top journals in basic scientific research continues to grow. The number of research papers led or co-led by Chinese research teams that were published in the three top academic journals including *Nature*, *Science,* and *Cell* increased from 61 in 2015 to 150 in 2020, with CAGR of 19.7%. At the same time, the papers published in top journals in basic research registered a growing influence. The total number of citations to papers published by Chinese research teams in the three top academic journals rose from 52,944 in 2015 to 140,131 in 2020[3]. In terms of professional publications for drug research and development, the 218 and 512 papers were published by Chinese research teams in JMC[4]and EJMC[5], respectively, compared with 76 and 203 in 2015, with a CAGR of 23% and 20%, respectively.

Figure 3: Rapid increase in the number of highly cited researchers in the biopharmaceutical field in China in recent years

Highly incited researchers in the biopharmaceutical fields[1] in Mainland China and their institutions in Top 1% in the World ESI

2015		2019	
Researcher	**Institution**	**Researcher**	**Institution**

[3] Web of Science
[4] Journal of Medicinal Chemistry
[5] European Journal of Medicinal Chemistry

Hongbin Shen	Shanghai Jiao Tong University
Chen Dong	Tsinghua University
Hualan Chen	Chinese Academy of Agricultural Sciences
Jun Wang[2]	BGI
Jian Wang	BGI
Huanming Yang	BGI

Wanqing Chen	National Cancer Center, Cancer Hospital Chinese Academy of Medical Sciences
Xing Chen	China University of Mining and Technology
Yan Deng	Hunan University of Technology
Caixia Gao	Institute of Genetics and Developmental Biology, CAS
Fu Gao	Institute of Microbiology, CAS, and Chinese Center for Disease Control and Prevention
Nongye He	Southeast University
Yong He	Beijing Normal University
Chiye Hu	Shenzhen Institute of Mental Health and The University of Hong Kong
Song Li	Hunan University of Technology
Chengfeng Qin	Institute of Military Medicine, Academy of Military Sciences PLA China
Jinhui Wang	South China Normal University
Yilong Wu	Guangdong Lung Cancer Institute
Junhua Li	BGI
Jian Wang[2]	BGI
Xun Xu[2]	BGI
Huanming Yang[2]	BGI
Ning Yan	Tsinghua University (now at Princeton University, USA)
Dequan Ye	The Chinese University of Hong Kong (Shenzhen)
Liping Zhao	Shanghai Jiao Tong University
Hao Zhou	Chinese PLA General Hospital
Quan Zou	University of Electronic Science and Technology of China
Xi'nian Zuo	Institute of Psychology, CAS

1.There are 8 sub-disciplines including Biology and biochemistry, Clinical medicine, Immunology, Molecular biology & genetics, Microbiology, Neuroscience & behavior, Pharmacology & toxicology, Psychiatry / psychology behavior, Pharmacology & toxicology, Psychiatry / psychology.

2.Jun Wang, Jian Wang, Xun Xu and Huanming Yang were all listed in the two sub-disciplines including Biology and Biochemistry and Molecular Biology & Genetics.

Source: Web of Science

Increase in the number of patents: China is leading the rankings worldwide in the number of patents related to pharmaceutical innovation. According to the Statistics of *World Intellectual Property Indicators* published by the World Intellectual Property Organization, China ranked among the top three countries globally with 8,619 biotechnology patents granted, 7,104 drug patents granted and 7,503 medical technology patent applications filed in 2019. [6]. From the

[6] WIPO Statistics Database

perspective of global proportion, the number of global patents China contributed to was also on the rise. The global share of China's patent applications related to pharmaceutical innovation (including biotechnology, pharmaceuticals, and medical technology) has increased from 25.0% in 2015 to 29.2% in 2019.

Accelerated development of emerging fields: the emerging field of biotechnology coincides with the rapid development of basic biopharmaceutical research in China despite the fact that it has a short rising period of development. The number of papers and patents in many such fields as stem cells, synthetic biology, and gene editing in China has entered the tier 1 of the world, which belong to the field of basic research with the smallest gap between China and the US.

China's basic biopharmaceutical research still lags behind the global leading level

China's basic biopharmaceutical research is still below the global leading levels although it has seen promising findings. Thus, more breakthroughs are needed to provide the source of pharmaceutical innovation. The comparison with international levels and quantitative analysis on key inputs and research outputs indicate that basic biopharmaceutical research in China still suffers from low proportion of basic research funding, limited number of top scientific research institutes, significant gap in the size of leading talents, room for improvement in proportion of high-quality papers, and insufficient translation and licensing of pharmaceutical patents. "The key core technologies are not available, cannot be bought and cannot be obtained." Only by mastering the capacity of make lighthouse-like discoveries in basic science, can China's pharmaceutical innovation take a new step and contribute to the source of global pharmaceutical innovation.

1. Room for improvement in high-quality cutting-edge research

Low proportion of high-quality papers: the number of papers published in the biopharmaceutical field in China has shown a rapid increase at a CAGR of 14.3% from 2015 to 2020, ranking consistently second in the world. Nearly 290,000 papers were published in 2020. However, as measured by the proportion of the number of papers published in *Nature*, *Science* and *Cell* to the overall number of papers published, the proportion of 0.17% for China significantly lags behind the level of leading pharmaceutical countries in Europe and the US, which is generally higher than 0.6%. Compared with top academic journals, a similar gap exists in the proportion of papers published in high-quality journals between China and leading pharmaceutical countries in European and the US. According to the journal quartile of the National Science Library, CAS[7], top 5% journals with the highest average impact factor in three years belong to Q1, of which there are a total of 51 high-quality journals with impact factors greater than 10 in general and biological categories[8]. In 2020, 1.5% of the papers in the pharmaceutical field were published in such high-quality journals in China, which is still at a low level compared with the proportion of generally higher than 3.0% in leading countries in European and the US.

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[7] *The Journal Citation Reports* (JCR), published annually by the American Science Information Institute, defines an impact factor index for major journals worldwide. In the journal quartile of CAS, all journals in JCR are classified into 13 categories, such as general and biology categories, and then they are divided into four classes based on impact factors, with the top 5% of the impact factors ranking as Q1, 6% to 20% as Q2, 21% to 50% as Q3, and the rest as Q4. The impact factor ranges from 2 to 45 in 80 journals in Q1 of general and biology categories.

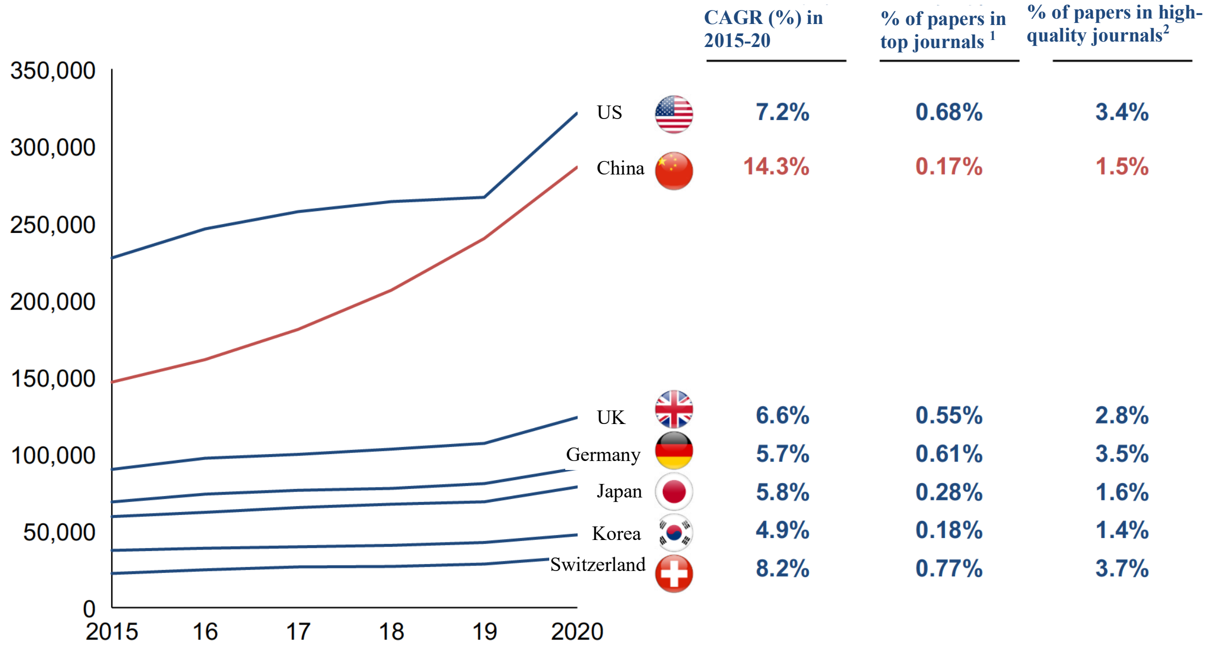
[8] Including 5 in general category: Nature, Science, National Science Review, Science Advances, Nature Communications; 46 in biology category

Insufficient influence of high-quality journals: 7 general and 73 biological journals totaling 80 are included in the Q1 journals in the CAS journal quartile. And there are 2 and 11 journals sponsored by China respectively, totaling 13 journals, and only 5 journals with impact factors >10. In contrast, 18 of 30 and 22 of 25 journals that have an impact factor of >10 are published in the US and the UK, respectively. In terms of the number of high-quality journals sponsored and relevant academic impact, there is still a large room for improvement in China compared to those of traditional dominant countries.

Give priority to follow-up in hot Research Fronts: based on the Research Fronts in the ESI database, the top 10 hot Research Fronts in the field of biological sciences in 2020 were selected by the CAS Institutes of Science and Development (CASISD), National Science Library, CAS and Clarivate. For instance, the research front of "targeted degradation of protein by small molecular PROTACs" has begun to move towards commercialization, and there are 3 highly cited core papers contributed by China, accounting for 7% of all core papers, which is far lower than that of the US, the UK and other leading Western countries. In terms of citing papers, China produced 215 citing papers, accounting for 14% of all citing papers, indicating that China has increasingly carried out follow-up studies in this front. With regard to innovative knowledge of basic research, China still relies on obtaining output from leading countries, especially the US. Most of the basic areas of modern life sciences, especially basic cutting-edge theories and technological innovations, originate from the US. Improved innovations in China are generally made on the basis of existing products or existing technologies, with few original theories, technologies and products. There is no exception in basic fields in which China is a leader, such as stem cells, synthetic biology, gene editing, all of which lack originally disruptive theoretical discoveries and technological innovations. In terms of international cooperation on publications in the field of biotechnology, the US is the dominant partner of China, and it also takes the lead in most co-authored outcomes. For example, China has made extraordinary progress in gene editing technology in recent years, with the total number of papers and patents close to the US level. However, the core patents related to gene editing technology, especially CRISPR/Cas9, are basically in the hands of other countries.

Figure 4: The number of biomedical papers published by China is fast-rising, but the share of the number of papers in top and high-quality journals is relatively low

Total number of biomedical papers published by leading countries worldwide in 2015-20, N



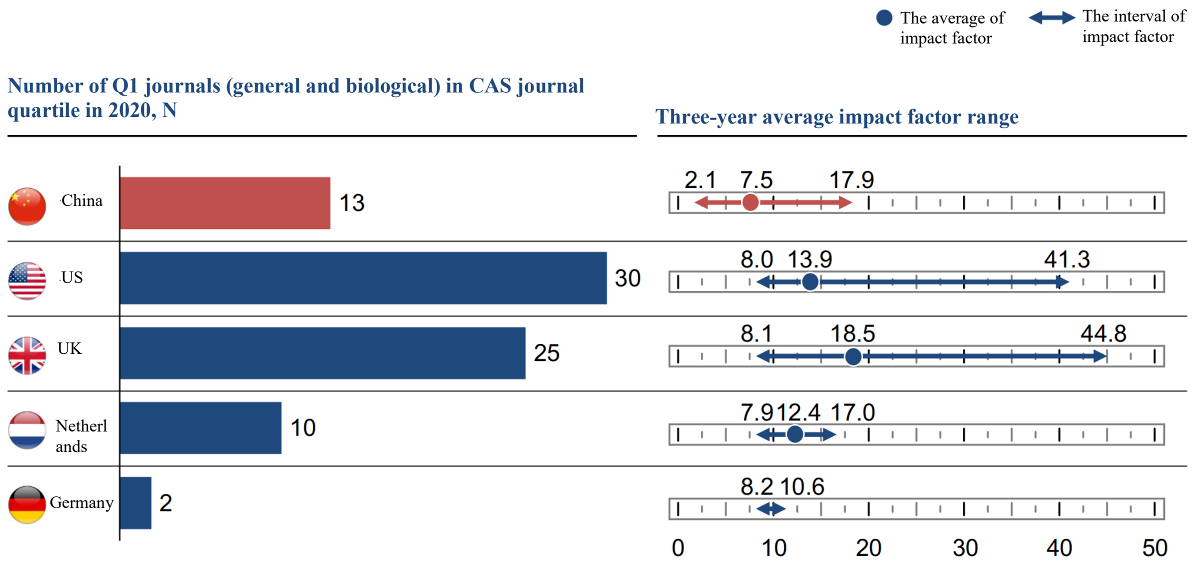
1. Including Nature, Science and Cell

2. Including 51 journals with an impact factor over 10 in general Q1 journals and biological Q1 journals in JCR quartile by CAS and covering the top journals. Specifically, including 5 journals with an impact factor more than 10 in general Q1 journals: Nature, Science, National Science Review, Science Advances, Nature Communications; 46 journals with an impact factor more than 10 in biological Q1 journals: Nature Reviews Molecular cell biology, Nature reviews genetics, Cell, Nature biotechnology, Nature Reviews Microbiology, Nature methods, Nature genetics, Annual review of biochemistry, Cell stem cell, etc.

Source: PubMed

Figure 5: In terms of the number of high-quality journals sponsored and relevant academic impacts in China, there is still room for improvement compared with those of traditional dominant countries

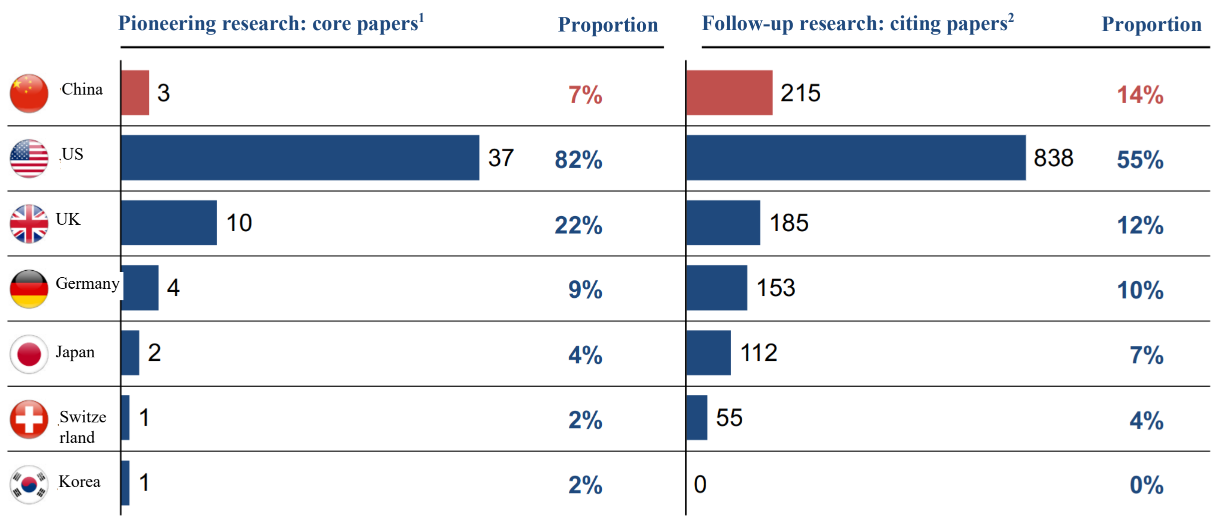
In terms of the number of high-quality journals sponsored and relevant academic impacts in China, there is still room for improvement compared with those of traditional dominant countries



Source: Journal Quartile Table of National Science Library, CAS

Figure 6: China has increasingly conducted follow-up research in hot Research Front biomedical research

2020 hot Research Fronts in biological sciences selected by ESI database: example of Research Front - "targeted degradation of protein by small molecular PROTACs"



1. By tracking the world's most significant scientific and scholarly literature and the patterns and groupings of how papers are cited—in particular, clusters of papers that are frequently cited together, "Research Fronts" can be discovered. When such a group of highly cited papers attains a certain level of activity and coherence, a Research Front is formed, with these highly cited papers serving as the front's foundational "core."

2. Literature citing core papers

Source: 2020 RESEARCH FRONTS; Institutes of Science and Development, Chinese Academy of Sciences, The National Science Library, Chinese Academy of Sciences, Clarivate.

2. Inadequate output of intellectual property transformation

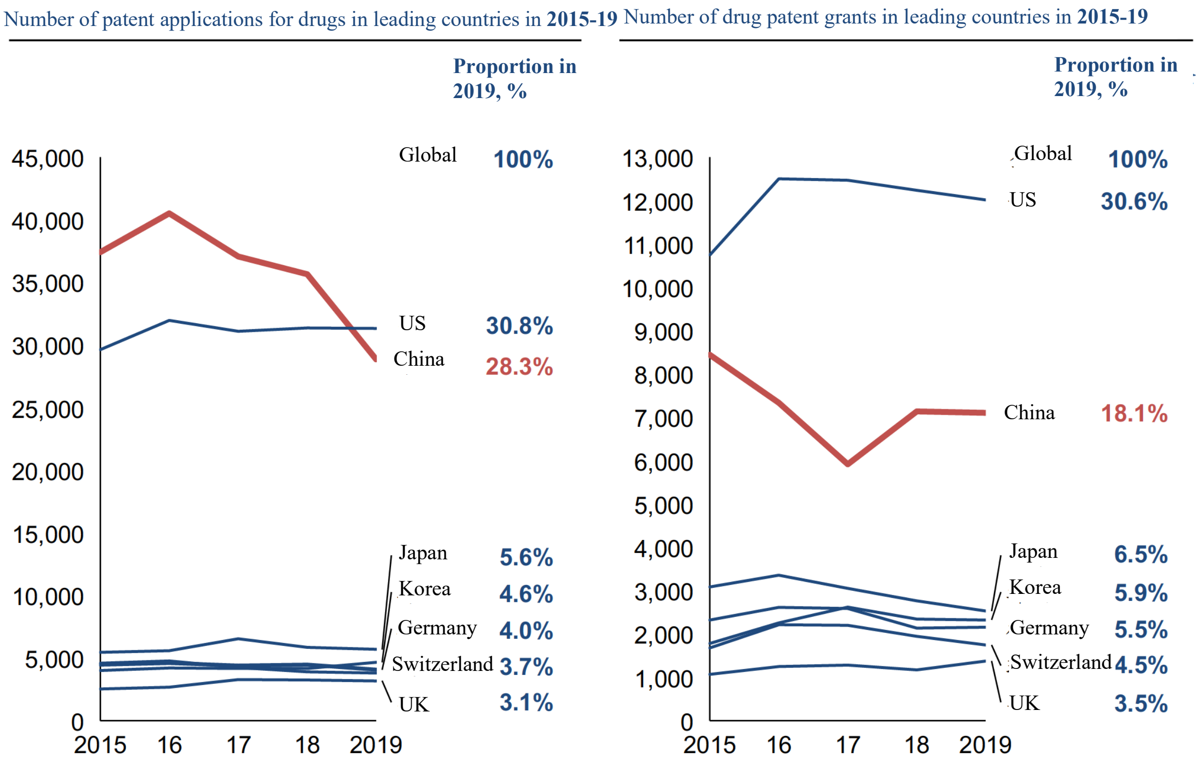
Low contribution of pharmaceutical patents: China has been ranking among the top two countries in the world in the number of pharmaceutical patent applications and grants in the past five years. Specifically, the proportion of pharmaceutical patent applications filed was 28.3% globally, while the proportion of pharmaceutical patents granted was 8.1% globally, with a relatively lower percentage of global contribution. In spite of high absolute number, the share of pharmaceutical innovation-related fields is still low with regards to the overall number of patent applications and grants in China. The number of patent applications and grants related to pharmaceutical innovation in China accounts for less than 7% of the total number of patents in China, which is still far from the 15-25% in Switzerland, the UK and the US.

Insufficient proportion of patent transformation: despite the large number of patents produced in China, the practice of transformation is yet to come, and it is relatively low in the proportion of scientific and technological achievements that are actually productized and commercialized. The *2020 China Patent Survey Report* shows that, among 735 colleges and universities and 381 R&D institutes surveyed, the implementation rate of valid invention patents is 14.7% and 28.9% respectively, lower than the patent conversion rate of about 37% in high-level universities in the US.[9]

Considerable intellectual property deficit: China's intellectual property exports have grown rapidly in recent years at a five-year CAGR of 57%, reaching $6.65 billion in 2019[10]. But China's revenue of intellectual property export is still lower than that of the world's leading countries from a global perspective. On the contrary, the import of intellectual property in China reached $34.33 billion in 2019, ranking second in the world. With an intellectual property export/import ratio of only 0.2, China has run a considerable trade deficit in the intellectual property sector.

[9] The licensing and selling of inventions by US universities
[10] WTO database

Figure 7: China has ranked among the top two countries in the world in the number of pharmaceutical patent applications and grants in recent years

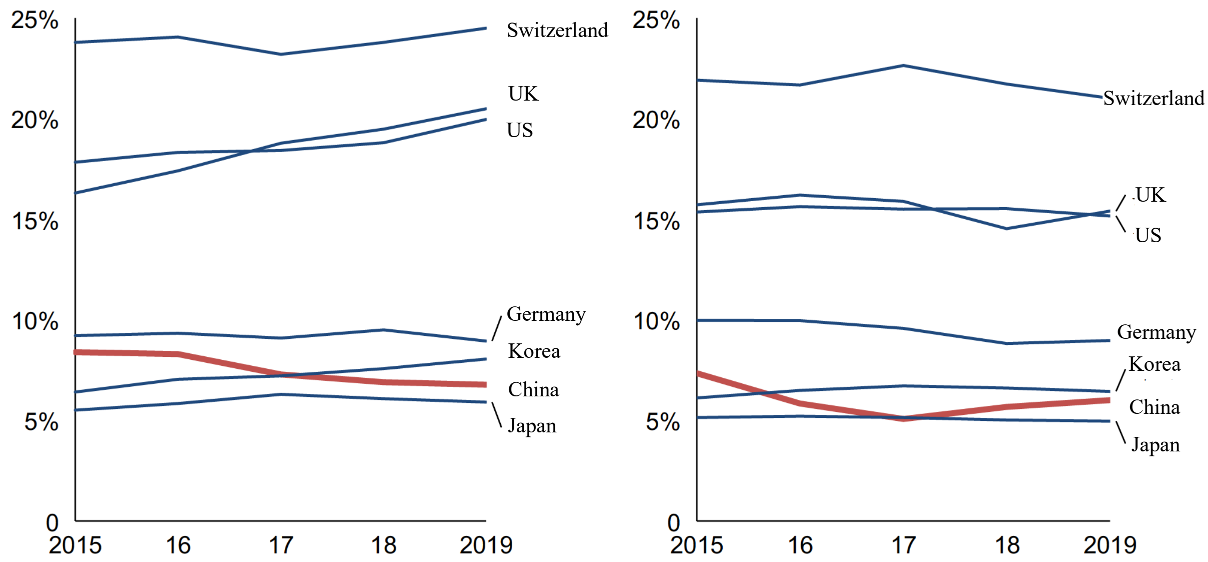


Source: WIPO Statistics Database

Figure 8: Compared to leading countries in Europe and the US, the patents related to pharmaceutical innovation in China registered a low percentage in the total number of domestic patents

Proportion of pharmaceutical innovation-related[1] patent applications to overall patent applications in global leading countries in **2015-19**

Proportion of pharmaceutical innovation-related[1] patent grants to overall patent grants in global leading countries in **2015-19**



1. Including biotechnology, pharmaceuticals and medical technology

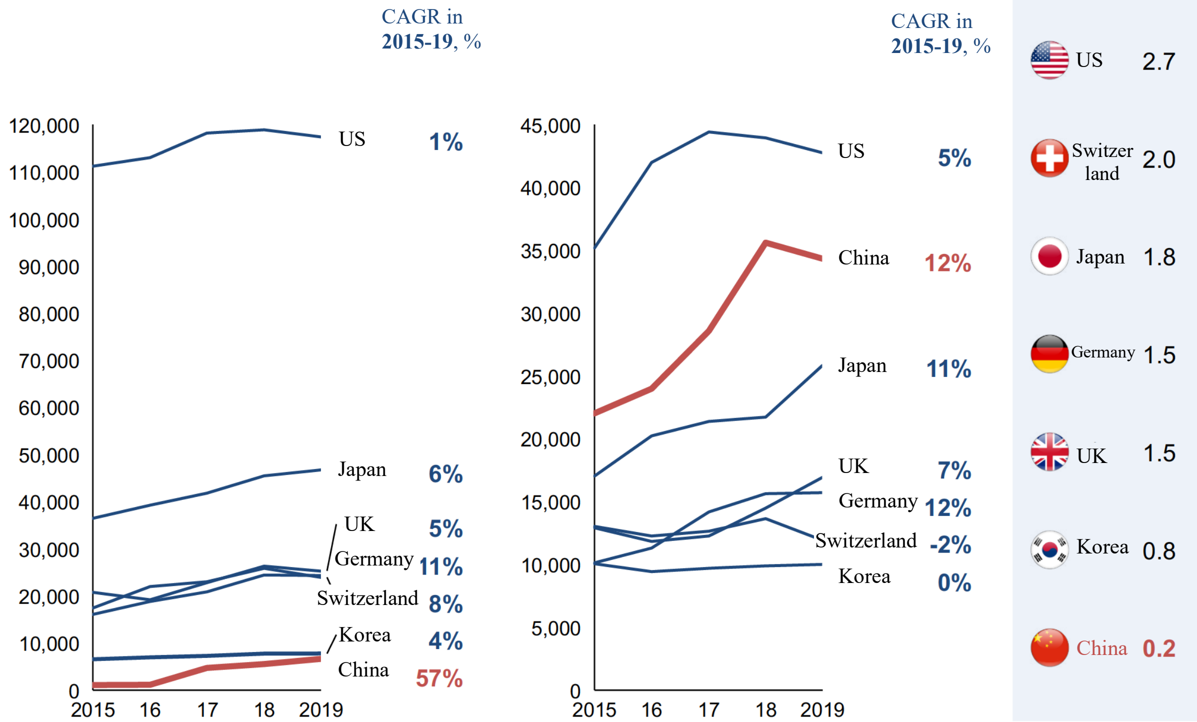
Source: WIPO Statistics Database

Figure 9: China's intellectual property exports have shown rapid growth in recent years, but are still far below those of leading countries

Export of charges for the use of intellectual property (namely revenue) in global leading countries in **2015-19**, million dollars

Import of charges for the use of intellectual property (namely expenditure) in global leading countries in **2015-19**, million dollars

Intellectual property export/import ratio in **2019**



Source: WTO database

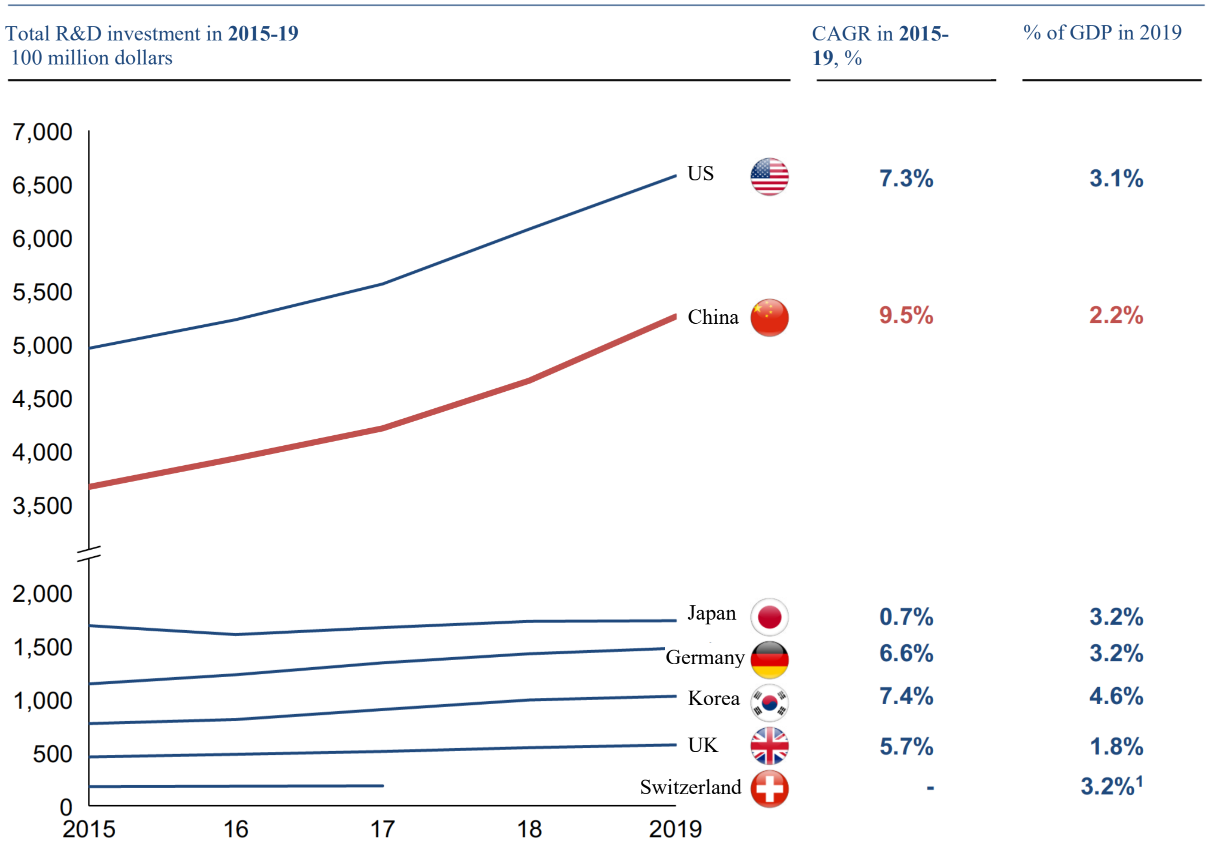
3. Unreasonable distribution at funding stages

Considerable scale of R&D investment: China's total R&D investment is second only to that of the US, consistently ranking the second place in the world in recent years. In terms of GDP ratio, it is slightly lower than the investment level of about 3% in leading biopharmaceutical countries in Europe and the US and the ratio is basically comparable.

Low share of basic research: In terms of funding sources, the share of R&D investment from the government is similar to that of global biopharmaceutical leaders, which is generally above 20%. From the perspective of the use of funds, although the ratio of investment in basic research in total R&D investment in China reached 6% in 2020, there is still a significant gap with the level of over 15% generally in leading biopharmaceutical countries around the world; similarly, the ratio of investment in applied research in total R&D investment in China at 11% is also far behind the average level of nearly 20% in global leading biopharmaceutical countries.

Lack of funding for incubation and transformation: according to the PitchBook database, the cumulative amount of venture capital investment in Chinese pharmaceutical and biotech projects at all stages has exceeded 23 billion dollars between 2016 and 2020, 99.5% of which was invested in Series A and subsequent rounds. Only 0.5% was invested in funds for seed and angel rounds that were used to support the industrial translation of basic research findings and the incubation of conceptual projects, with the proportion of deal counts of 7.4%, which was far lower than the proportions of investment amount (generally >4%) and deal counts (>35%) in leading European countries and the US.

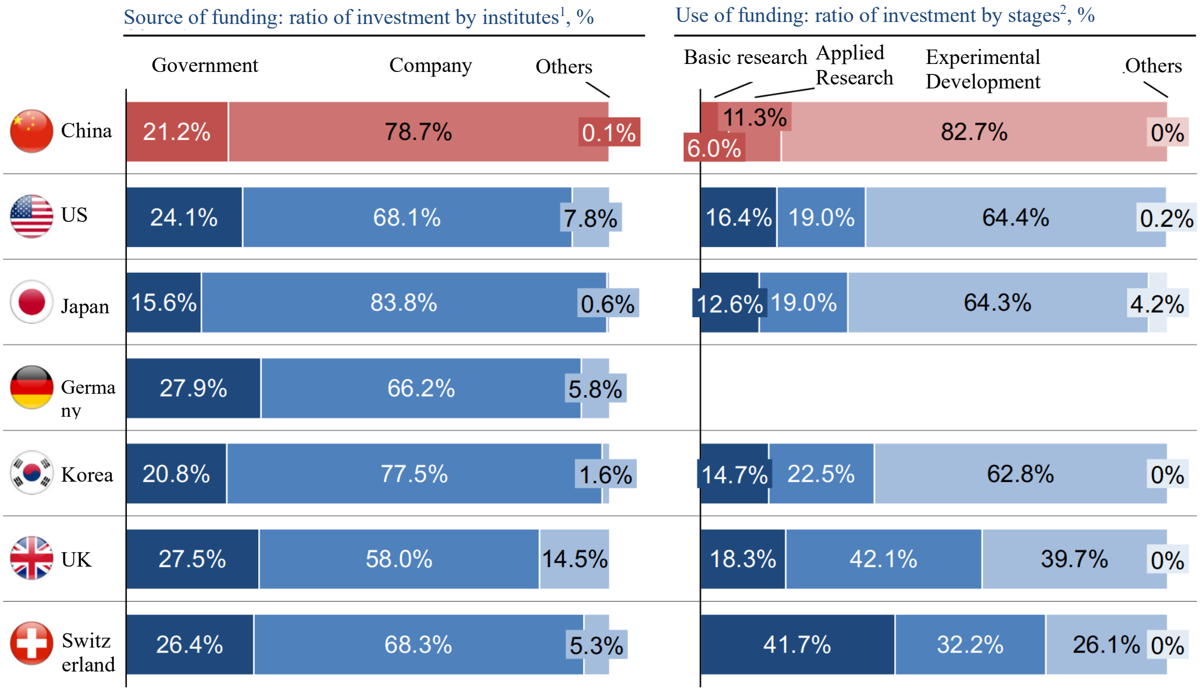
Figure 10: Steadily ranking second globally, the ratio of R&D investment to GDP in China is comparable to that of global leading biopharmaceutical countries



1. 2017 data (for Switzerland as the latest data available)

Source: OECD database

Figure 11: The sources of China's R&D funding is comparable to those of global leading biopharmaceutical countries, investment in basic research yet to strengthen

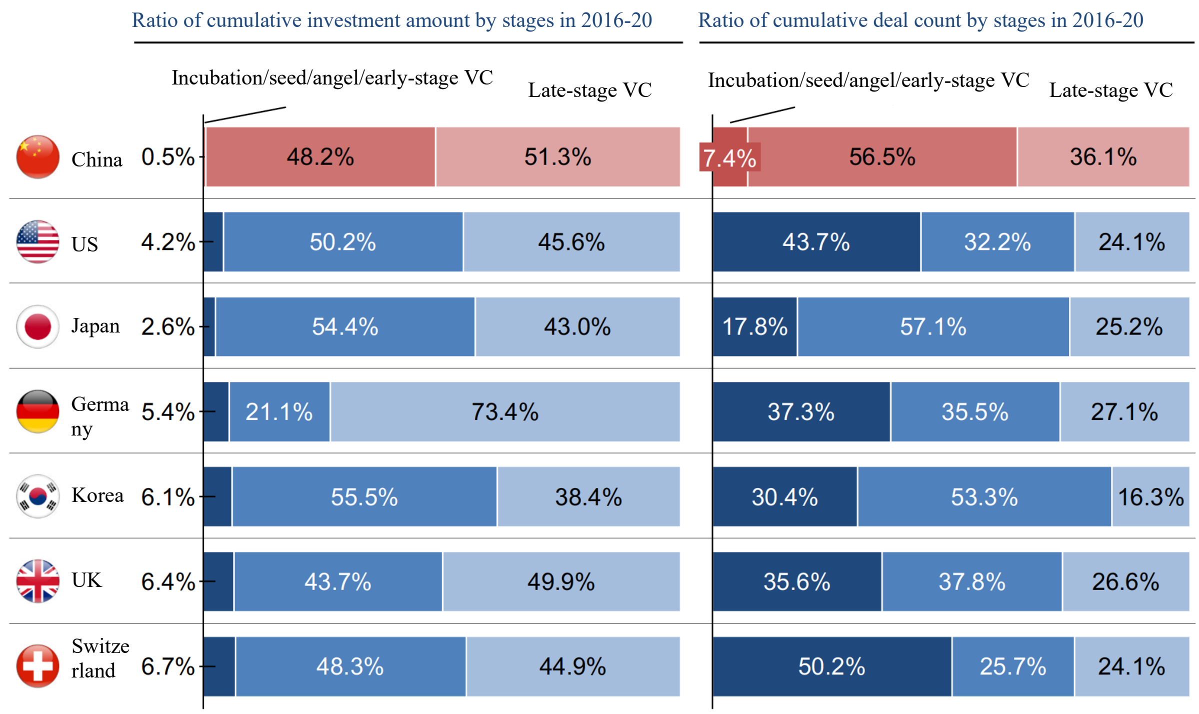


1.2019 data (the latest data available in 2018 for US, Germany and UK, the latest data available in 2017 for Switzerland)

2.2019 data (the latest data available in 2018 for Japan and UK, the latest data available in 2017 for Switzerland)

Source: OECD database

Figure 12: Ratio of venture capital funding used to support incubation and transformation in China is much lower than that of global leading biopharmaceutical countries



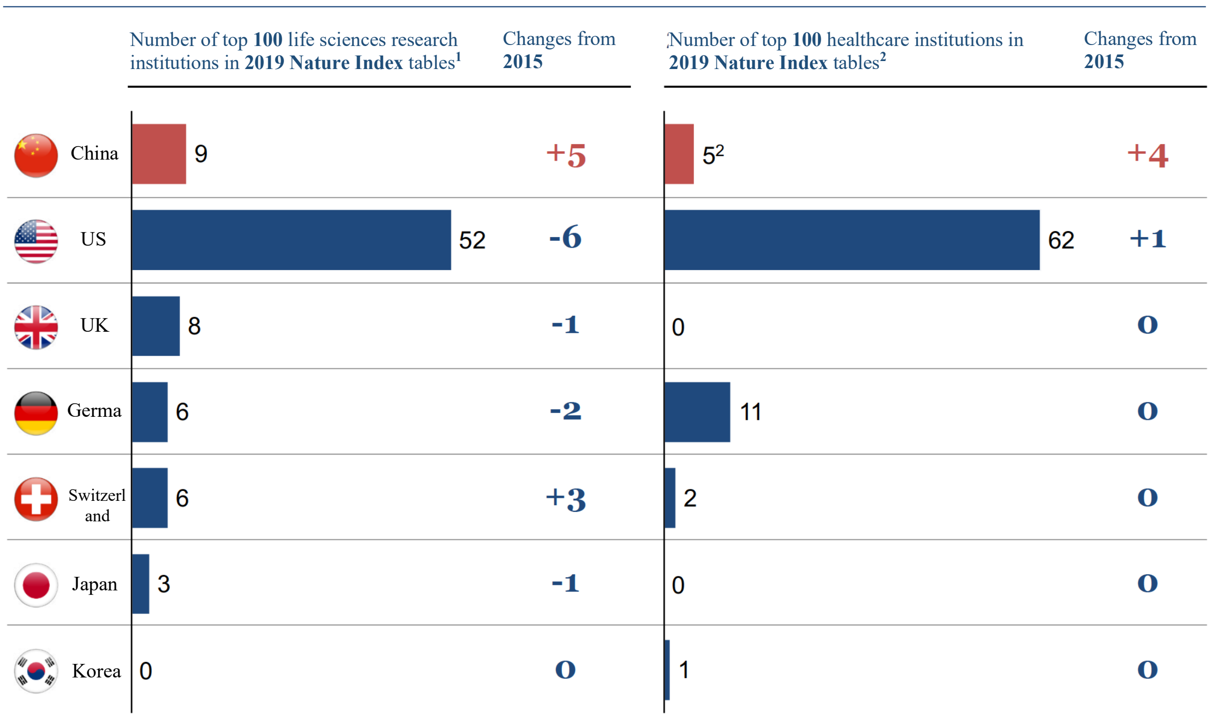
Source: PitchBook database

4. Limited number of top research institutions

Institutions for life sciences: The United States has the largest number of top institutions for life sciences in the world. In the Nature Index tables of global top research institutions in life sciences that reflects high-quality research outputs, U.S. institutions dominated half of the top 100 in 2019, with 52 institutions in the table; China came in second with a significant improvement from its fourth place in 2015, although only 9 institutions ranked in the table.

Academic healthcare institutions: Among the world's top healthcare institutions, U.S. academic medical centers are more notable for their leadership in research capacities. In the Nature Index tables of global healthcare institutions that reflects high-quality research outputs, U.S. institutions took the absolute leadership with 62 of the top 100 in 2019. Germany ranked second with 11 institutions on the list. China had five institutions on the list in 2019, in order of ranking: West China Hospital (26th), Renji Hospital (31st), Sun Yat-sen University Cancer Center (56th), Xiangya Hospital (75th) and Zhongshan Hospital, Fudan University (79th). In 2015, only West China Hospital was on the list.

Figure 13: Compared with the number of top life sciences and healthcare institutions in the U.S., there is still great room for improvement in China



1. Reflects high-quality output based on publications in 82 high-quality natural science journals

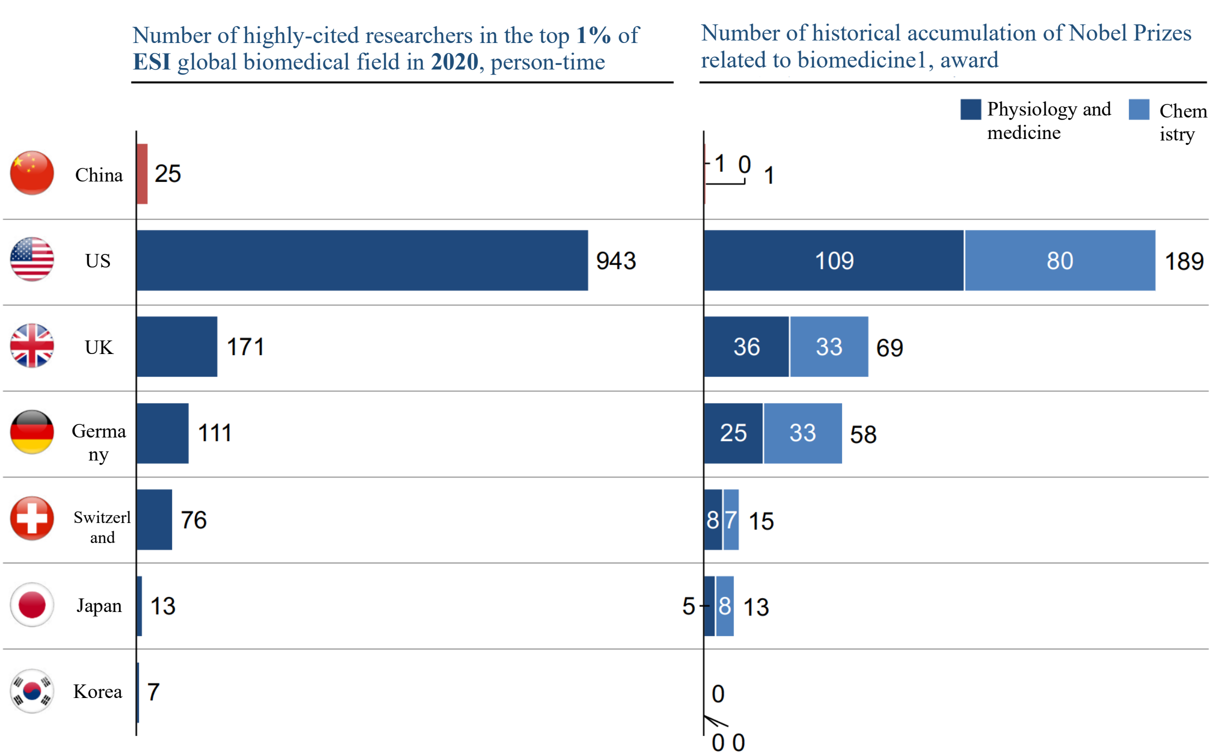
2. West China Hospital, Renji Hospital, Sun Yat-sen University Cancer Center, Xiangya Hospital and Zhongshan Hospital, Fudan University. In 2015, only West China Hospital was on the list.

Source: Nature Index

5. Significant gap in leading talents

Significant shortage of leading talents: Leading talents and teams are still scarce in China despite the growing base number of biomedical researchers. In terms of historical accumulation of top talents, Japan, also an Asian country, has won 13 Nobel Prizes related to biomedicine (physiology and medicine, chemistry) in total, much higher than China. From the perspective of the current status of high-level talents, there are 1,790 person-times in total of highly-cited researchers in the top 1% of ESI global biomedical field in 2020, among which the U.S., U.K. and Germany ranked top three, with 943, 171 and 111 respectively, accounting for nearly 70% of the total, while China had only 25 person-times on the list[11].

Figure 14: In terms of the number of biomedical leading talents, there is a significant gap between China and leading countries



1. Physiology and medicine, chemistry
Source: Web of Science; Nobel Prize

[11] Since three researchers are listed in two sub-disciplines, the actual number of researchers on the list is 22

Chapter 2

Major Challenges to Enhance the Capacity for Basic Research as the Source of Innovation

Basic research is a key element in providing the source of pharmaceutical innovation

Strengthening basic research to promote pharmaceutical R&D requires the direction guidance of national strategic planning (NSP) and overarching design, as well as the implementation support of a series of key elements and institutional environment. The NSP guides the direction of basic research, and sets the goal of providing the source of original innovation for pharmaceutical R&D. Key elements take over the strategic planning and support the implementation of basic research, including four aspects of funding, core resources, innovators, and talent structure. Specifically, funding guarantees the provision of the various hardware and software resources required for basic research; core resources provide the necessary input for the development of various types of basic research; innovators are the core organizations engaged in the conduct of basic research and the output of basic research findings; and talent structure is the prerequisite to ensure the various human resources and knowledge accumulation required for basic research. A favourable institutional environment in turn integrates key elements, creates a positive cycle, optimizes resource allocation and stimulates system vitality.

Major constraints faced by key elements

1. Funding stages and allocation efficiency constrain the source of innovation

Relatively insufficient investment in the source of innovation: All links of the biopharmaceutical R&D value chain require sufficient and continuous financial support to bridge basic research and industrial translation and thus form an innovation chain. Despite the massive influx of capital into the pharmaceutical innovation sector, with record amount of funding and R&D investment, structural mismatch can be found along the value chain, preventing the formation and connection of the innovation chain. In terms of the distribution of funding stages, more than 80% of China's total R&D investment is spent on back-end experimental development, and the funding for basic research is disproportionate to its key position, consequently, the relative lack of funding at the source end of the innovation chain restricts the emergence of a large number of original innovations; in terms of the types of funding sources, public investment supports basic research, and venture capital (VC) and private equity (PE) funds support industrial development, but both public investment and early VCs have failed to effectively support the initial stage of industrial translation of basic research findings. The lack of high-tolerance patient capital and seed funds and the financial fault in the innovation chain likewise constrain the findings in scientific research from acting as the source of innovation.

Government investment needs to be integrated for enhanced efficiency: On the one hand, the current level of resource integration of public investment is insufficient. Although China has integrated to form the new five categories of science and technology (S&T) plans, the specific management of S&T projects in the national S&T plan system is still carried out separately by different departments and bureaus of the Ministry of Science and Technology. While formal integration of resources has been achieved, in practice there is still decentralized hierarchical management. In the field of biomedicine, China has not had a dedicated national biomedical fund, nor a corresponding professional management agency in the field of biomedicine. On the contrary, leading biomedical countries in the world such as the U.S., U.K., Japan all have established national biomedical funds with highly integrated resources and professional management agencies with high professional capacity in the biomedical field to undertake the national will and implement national strategies at the funding level.

On the other hand, the efficiency of resource allocation of government funds at the basic research end and the industrial translation end needs to be enhanced. At the basic research end, a fair and efficient mechanism for allocating and managing research funds has yet to be developed to encourage long-term, novel and pioneering original innovation, and to avoid over-investment in large-scale equipment and blind re-investment and waste of resources in hot areas. At the industrial translation end, a large amount of government funds is piled up in late stage projects with short-term predicted returns, with insufficient patience and tolerance, and this reflects that the efficiency of policy inclination and selection support for early industrial translation of high-quality basic research findings still needs to be improved.

2. Risk of "being hit in the throat" in the production and supply of core resources

Biomedical information and data storage and standards: In the past decade, research in the life sciences has gradually shifted to a data-intensive approach. This shift has been driven most notably by the vast amount of data that has been accumulated through deeper research in genomics, proteomics, transcriptomics, and other "omics", and the complex interconnections of living entities that these data represent pose an enormous challenge to new scientific discovery. The high-throughput sequencing data stored at the National Center for Biotechnology Information (NCBI) has grown exponentially over the years. However, in the absence of a unified biomedical data platform in China, our researchers have to access biomedical data from NCBI for life sciences related research.

High-end laboratory equipment required for basic research: As for the key equipment for biotechnology research, the commonly used nuclear magnetic resonance equipment, high-resolution mass spectrometry and other large analytical instruments, as well as the majority of the life sciences instruments such as magnetic resonance imaging equipment, super-resolution fluorescence imaging equipment, cryo-transmission electron microscope, etc. are heavily dependent on imports.

Reagents, materials and laboratory animals required for basic research: China relies heavily on imports of reagents and consumables for research in the life sciences and medicine. The market share of local brands is only 5%-10% in the markets of either biochemical reagents, molecular reagents, cellular reagents, antibodies or instrument consumables. The U.S. is the leader in the field of laboratory zoology with more than 200 laboratory animal species resources, more than 26,000 genetically engineered animal strains, and more than 10,000 disease animal model resources. In terms of total laboratory animal resources, China has only 30 laboratory animal species, less than one-sixth of those of the U.S.; in terms of laboratory animal strains such as genetically engineered animals, genetically diverse animals, mutant strains, etc. China has only 3,000 strains, less than one-eighth of those of the U.S. Novel animal models that are important for human disease and drug development, such as RasH2 transgenic mice and NOG immunodeficient mice, have also been successfully developed by developed countries first, while China relies on introduction or imitation.

3. Mechanism and evaluation orientation of innovators constrain innovation vitality

Bias of scientific research evaluation mechanisms in universities: Influenced by past evaluation indicators, the "four prevails" phenomenon of "paper prevails, title prevails, education background prevails, award prevails" is very common in universities. The trend of "paper prevails" is particularly prominent, causing the loss and bias of scientific research values. In university evaluation systems including project evaluation, talent evaluation, institutional evaluation, resource allocation, performance assessment and others, the indicator of papers is common because of its simplicity and ease of use, but it can easily lead to simple and rough evaluation methods and one-sided and inappropriate evaluation criteria, making it difficult to play the positive guiding role of "baton". In February 2020, the Ministry of Science and Technology and the Ministry of Finance jointly issued the 'Several Measures for Eliminating the Negative Orientation of "Paper Prevails" in Science and Technology Evaluation (Interim)', which was intended to eliminate the negative orientation of over-valuing the number of papers and high impact factors in science and technology evaluation, while ignoring the finding quality and actual contributions. However, the "four prevails" have been eliminated but the establishment of a multidimensional and scientific evaluation system still needs to be explored.

Today "paper prevails" has brought about the blind pursuit of short-term paper output and the lack of attention to long-term original innovation, while what the basic research needs are to open up new fields, ensure continuous investment and insist on long-term dedication in order to produce lighthouse scientific achievements. Most of the research in universities under the orientation of "paper prevails" focus on low-risk topics with clear outputs, such as exploration of known targets, which is difficult to generate source innovation.

At the same time, the "paper prevails" approach has also resulted in the insufficient translation of basic research findings with industrial application potential. It is still common for universities to emphasize basic research over applied research and papers over the finding translation, and they do not understand the market and the needs of enterprises, and also lack the motivation of innovation transformation. The capacity and willingness of universities to build a sound intellectual property trading and management mechanism is insufficient, and the incentive policies and implementation measures for technology transfer and industrialization of the results of researchers are weak. According to the *2020 China Patent Survey Report*, 26.8% of universities and 15.6% of research institutions have established provisions or actual practices related to the division of ownership for service inventions or other scientific and technological achievements.

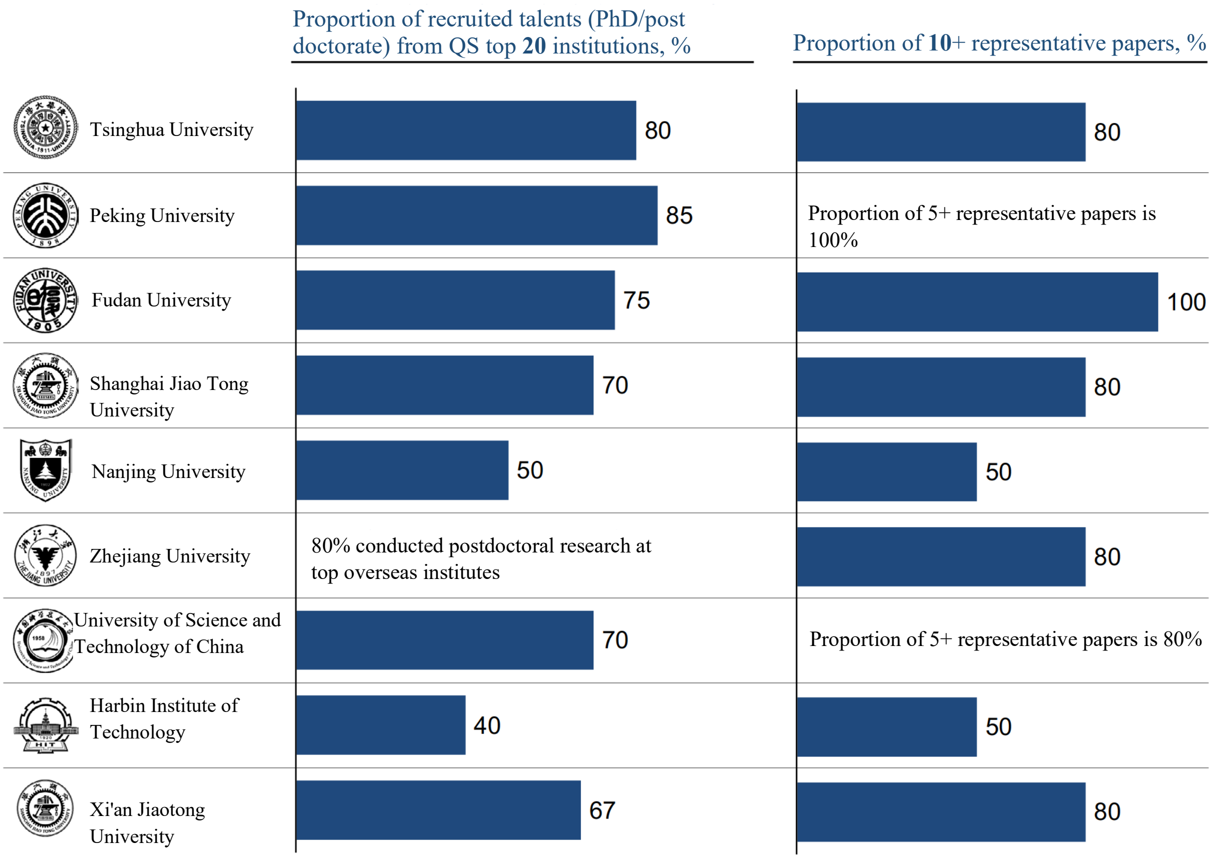
Insufficient translational research in healthcare institutions: Academic healthcare institutions with research capacities in China are often tasked with heavy healthcare services, and the focus of doctors is mainly on clinical care. At the same time, the talent evaluation system of healthcare institutions also has a the trend of "paper prevails", and the dual pressure of clinical work and publication further reduces the incentive for doctors to engage in translational research related to pharmaceutical R&D. China actively focuses on the development of translational medicine and the construction of domestic translational medicine research centers is also flourishing; however, many translational medicine centers remain in name only due to capacity, resources, mechanism and other factors, and there is still a long way to go in the two-way translation of "from laboratory to hospital bed" and "from hospital bed to laboratory".

Limited industry-university-hospital-research cooperation: An innovation ecology with mutual integration has not yet been formed among innovators because of the insufficient project cooperation and flow of personnel between universities and research institutions, medical institutions and enterprises. In terms of exchange between hospital and research institution, the development of basic research and clinical practice is unbalanced, and although partial cooperation has been formed, the exchange between basic and translational researchers is not sufficient and profound, leading to ineffective integration of the advantageous resources of clinically oriented medical research; in terms of industry-universities cooperation, the early collaboration between academia and industry is still relatively limited as many enterprises are confined to the risks and their own R&D priorities and pay less attention and investment to the basic and translational research about discovery of new mechanisms and targets.

4. Capacity structure and evaluation mechanism of talents limit innovation supply

Fierce competition for top talents: Top talents and teams are still scarce in China despite the growing base number of researchers. The number of highly-cited researchers in the top 1% of the ESI global biomedical field in China is only 1/38 of that in U.S., 1/7 in U.K. and 1/4 in Germany, which is a constraint to the development of groundbreaking and leading research. At present, the reliance on high-level overseas talents for the introduction of talents in China's top universities is still high. The majority of the faculty members recruited by the C9 League in the past five years have experiences in top overseas research institutions, and more than 70% of talent recruited by most League members are from the QS top 20 institutions. The talent arms race among the world's leading countries has been unprecedentedly intense, and they have escalated attracting global talents to a national strategy. To cope with this long-term challenge in China, which is a traditional talent-exporting country, how to attract overseas talents to return to China and keep, train and motivate available high-level talents is the basis for enhancing basic research and the source of pursuing source innovation.

Figure 15: The majority of the talents recruited by China's top universities in recent years have experiences in top overseas research institutions



The talent evaluation mechanism needs to be improved: An increasing number of universities have started to adopt a tenure-track system, in which mid-term and final appraisals are set in the third and sixth years, respectively, to decide whether to employ a faculty member on a permanent basis, based on their scientific output. Although the tenure-track system provides additional motivation for researchers, the applicability to certain areas of research is still questionable. Basic and original scientific research often takes long time, and an assessment mechanism that uses short-term quantitative outputs over 3-6 years as the main evaluation indicator tends to lead researchers to choose research topics that can be published in short term, rather than engaging in directions that are important but require long-term dedication. The key to further encouraging talent development and promoting innovation is to improve the existing talent evaluation mechanism and to take into account long-term research value orientation while providing effective incentives.

Insufficient inter-disciplinary talents to meet the demand: Pharmaceutical R&D involves multidisciplinary intersection, and the talents trained under China's existing biomedical education model often have in-depth attainment in one field, but there is an obvious shortcoming in multidisciplinary integration; pharmaceutical R&D also involves multi-sector intersection, which requires both expertise in academic sector and experience in establishing business laws and regulatory rules in industrial sector. China's existing talent training path cannot meet the demand for inter-disciplinary talents, resulting in a bottleneck of talent to carry out industrial translation in the country.

In terms of translational research talent, while there is a global shortage of translational talent, the challenges faced by China are particularly acute. First, basic researchers in universities often do not understand clinical needs and processes, and the design philosophy of scientific research protocols is different from that of early stage drug research; second, clinical researchers in healthcare institutions mostly have only medical background but scientific training is insufficient to promote the translation of basic research; and third, R&D talents with translational research capacities in the industry have many high-paid options and are less likely to engage in the industrial translation link with high risk and uncontrollable reward. The reason for this is closely related to the late start and insufficient supply of the source of inter-disciplinary talent training. In the case of MD-PhD programs designed to train medical scientists, most such programs at China's leading medical schools began in the 21st century, half a century behind the U.S. And it has not yet entered a period of rapid growth in terms of the number of programs, number of students, or academic arrangements and training pathways.

In the technology transformation departments of universities and research institutions, the lack of professional teams has become a major bottleneck in the industrial translation of research findings. According to the *2020 China Patent Survey Report*, 56.7% of participating universities and 43.5% of participating research institutions believe that the lack of professional teams for technology transfer is the biggest hurdle to the transfer and transformation of patents. At present, the technology transformation departments of universities and research institutions mostly perform administrative function with risk control as the major task. Due to the absence of professional technology managers, the team lacks the corresponding industrial experience to identify, discover and promote the basic research findings with the most translation value and application potential, neither forming professional judgments nor establishing a sound patent strategy or take the initiative to market the patent results.

Chapter 3

International Cases and Their Enlightenment

National strategic planning leads the research directions

Various world's leading biomedical countries have adopted overarching planning at the national level to clarify the strategic value of basic research and its translation in the pharmaceutical industry, sort out research focus areas and strategic priority projects, and lead the direction of national research and industrial development in real time through regular and systematic updates.

The U.K. launched Strategy for UK Life Sciences consecutively in 2011 and 2012 that clarified strategic objectives and overarching design, proposed areas of focus such as synthetic biology and cell therapy, indicated the strategic value of translational medicine infrastructure, clinical data, genetic data and biobank information systems, and had an independent Life Sciences Advisory Board to promote the implementation of strategic initiatives. Another Life Sciences Industry Report was launched consecutively in 2017 and 2018, which strengthened the role of life sciences research in shaping and driving industry development. Research focus areas and strategic priority projects have been clearly identified in strategic planning documents over the years, leading the way for input.

The U.S. has issued national strategic documents to promote biomedical research and pharmaceutical innovation from multiple perspectives over the past decade, including the 2012 Report on Propelling Innovation in Drug Discovery, Development, and Evaluation, the 2018 HHS Strategic Plan FY 2018 - 2022, and the 2021 Future Industry Development Report. The periodic and systematic overarching strategic design establishes the principle direction of maintaining the advancement of major countries.

High level of funding and scientific distribution

All leading biomedical countries around the world guarantee long-term, continuous, stable and high government fund investment on the one hand, and achieve scientific allocation in stages and fields through management by professional institutions on the other hand, aiming to stimulate a blossoming research ecology and coordinate the synergistic implementation of national strategic priorities.

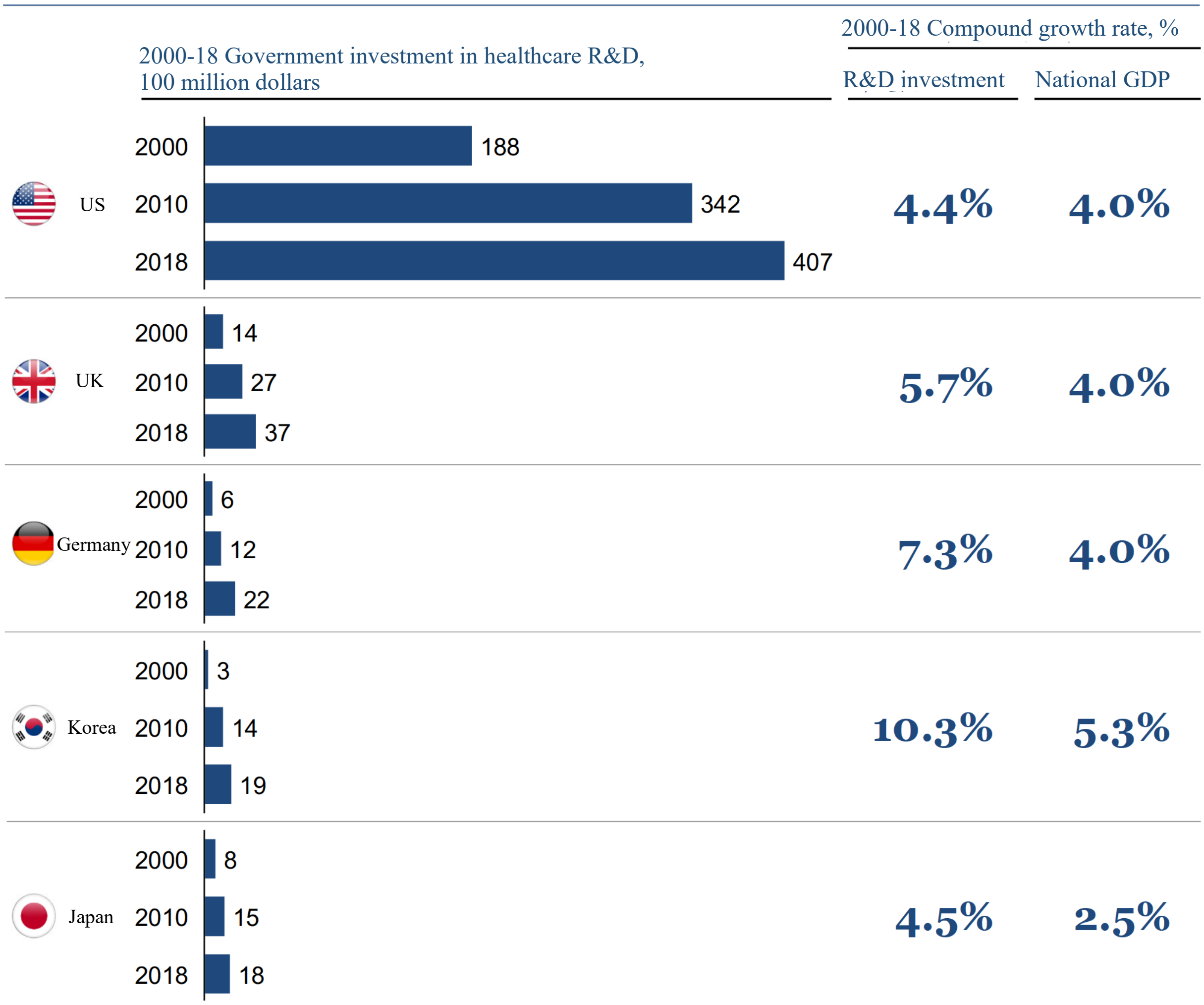
Scale of government investment: The U.S. is the world's largest investor in medical research, and the U.S. government invested $40.7 billion in healthcare R&D alone in 2018, and maintains an annual growth rate of 4.4% to secure its global top position[12]. The U.K., Germany, South Korea and Japan rank second to fifth, with government investment in healthcare R&D of $3.7, $2.2, $1.9 and $1.8 billion in 2018, respectively. The annual growth rate of Germany, South Korea and Japan are all at almost twice the annual rate of GDP growth, reflecting the importance the country attaches to healthcare R&D.

Unified distribution entity: Several leading countries have established professional institutions to guarantee the scientific use and distribution of government healthcare R&D

[12] OECD database

investment. In the U.S., the National Institutes of Health (NIH) oversees allocation of about 87% of government fund, with up to $41.7 billion in 2020. A competitive project-based research funding system empowers research institutions nationwide and promotes a blossoming innovation ecology; the establishment of a multi-level check-and-balance evaluation mechanism guarantees that resources are allocated to the most appropriate undertaking entities in a fair and reasonable manner. Statistically, 210 new drugs were approved by the U.S. Food and Drug Administration (FDA) between 2010-2016, and all new drugs had received NIH funding for their development[13]. More than 90% of these funds went to basic research related to the biological targets of drug action, rather than the drugs themselves. This shows the key position and key focused links of NIH in the pharmaceutical innovation and R&D in the U.S. In the U.K., the National Medical Research Council (MRC) and the National Institute for Health Research (NIHR), the leading biomedical research funding institutions, manage allocation of approximately 64% of government funds in total to support a wide range of biomedical research projects, as well as infrastructure development, through a competitive project-based mechanism[14].

Figure 16: Government investment in healthcare R&D in leading biomedical countries worldwide



[13] Contribution of NIH funding to new drug approvals 2010-2016
[14] UK Health Research Analysis 2018

Source: OECD database

Venture capital funds: Looking at the stage distribution of VC funds in leading countries in Europe and the U.S., it basically shows a trend that incubation and seed stage deals are the most active, and the number of projects gradually reduces with the investment stage. In the U.S., for example, the cumulative number of incubation/seed/angel round deals in the U.S. from 2016-2020 accounted for 43.7% of all VC deals, with early-stage VC deals accounting for 32.2% and late-stage VC deals accounting for 24.1%. Adequate public investment guarantees the generation of original innovations in basic research, from which mature social capital identifies and incubates early-stage concepts with market potential, assumes the high risk of initial investment, and also reaps generous returns from the commercial translation of breakthrough innovations into the market, feeding future investments.

Diverse innovators create a collaborative ecology

All leading biomedical countries around the world actively encourage the full exchange between innovators, especially between academia and industry, to connect the source of innovation and commercialization entities, and thereby promote the gradual formation and improvement of the industrialization chain, as well as the enhancement of innovators' own capacities.

The EU's Innovative Medicines Initiative (IMI) is by far the world's largest public-private partnership (PPP) platform in the pharmaceutical sector. Established in 2008 by the European Commission's Directorate-General for Research and Innovation and the European Federation of Pharmaceutical Industry Associations (EFPIA), the IMI has an overall budget of €5.3 billion to date. As an international collaborative platform among industry, universities and research, the IMI aims to accelerate the development of pharmaceutical and health research and innovation in Europe by funding projects. Prior to 2013, the aim was to improve the safety and efficacy of innovative drugs in the long term by significantly increasing the efficiency and benefits of drug development; while from 2014 onwards, in line with the EU's Horizon 2020 strategic framework, the aim is to accelerate innovative research that addresses urgent health challenges for society and patients.

In the U.S., the California Institute for Quantitative Biosciences (qb3), led by the State of California and founded in 2000, is a research institute as well as an entrepreneurial accelerator that aims to use quantitative science to integrate understanding of biological systems at all levels, address the most significant challenges in health, environment, and energy through unprecedented new discoveries, products, and technologies, and speed up the development of California's bioeconomy. It is led by campus research directors at three California universities (Berkeley, San Francisco, Santa Cruz), has 180 scientists participating in researches, and supports for startups with seed funding, incubation labs, etc. Diversified models of innovative business cooperation between enterprises and qb3 have been formed, such as innovation centers jointly established together with participating universities and joint investments in startups together with venture capital institutions, so that scientific discoveries in qb3 can be understood and applied in the first place and at a lower cost.

In Switzerland, the Federal Institute of Technology of Lausanne, the University of Geneva and two-family foundations launched Campus Biotech, a new collaborative innovation platform in Geneva in 2013, with the aim of maintaining Switzerland's position as a global leader in biotechnology and life sciences research. The micro-ecology of academic centers, clinical centers, startups, core facilities, and catalyst funds was built in a space of about 40,000 square meters to promote 15 research teams and dozens of startups to work side by side around the two main themes of neuroscience, and digital & global health to accelerate the transformation from theoretical research to product application.

Inter-disciplinary talents training for two-way flow

The world's leading biomedical countries strengthen their teams and cultivate a multi-level, multi-disciplinary talent pipeline that is responsive to the needs of pharmaceutical R&D innovation, mainly by attracting the excellent talents around the world and by training inter-disciplinary talents on their own. They also promote a rational two-way flow of talents by building a channel of talent exchange among academia, medicine and industry, so as to connect basic research, clinical needs and commercial applications.

In order to train medical scientists who can integrate scientific research and medical practice, the MD-PhD dual degree program was initiated in the U.S. in the 1950s, which has since offered over 90 programs with approximately 5,400 enrolled students currently[15]. To encourage the training and development of talents on a national scale, the NIH launched the Medical Scientist Training Program (MSTP) special fund in 1964. Currently, the MSTP reaches approximately 50% of the universities in the U.S. that offer MD-PhD programs, with a cumulative number of over 10,000 funded people. MD-PhD program graduates with both solid basic research experience and systematic knowledge of clinical medicine are often better equipped for R&D leadership roles in academic institutions, biotechnology enterprises, and pharmaceutical enterprises than graduates with a single training in either basic science or clinical medicine. About 60% of the research work of MD-PhD graduates is related to translational research and 50% to basic research, providing a sustained core driver for pharmaceutical innovation in the U.S.[16].

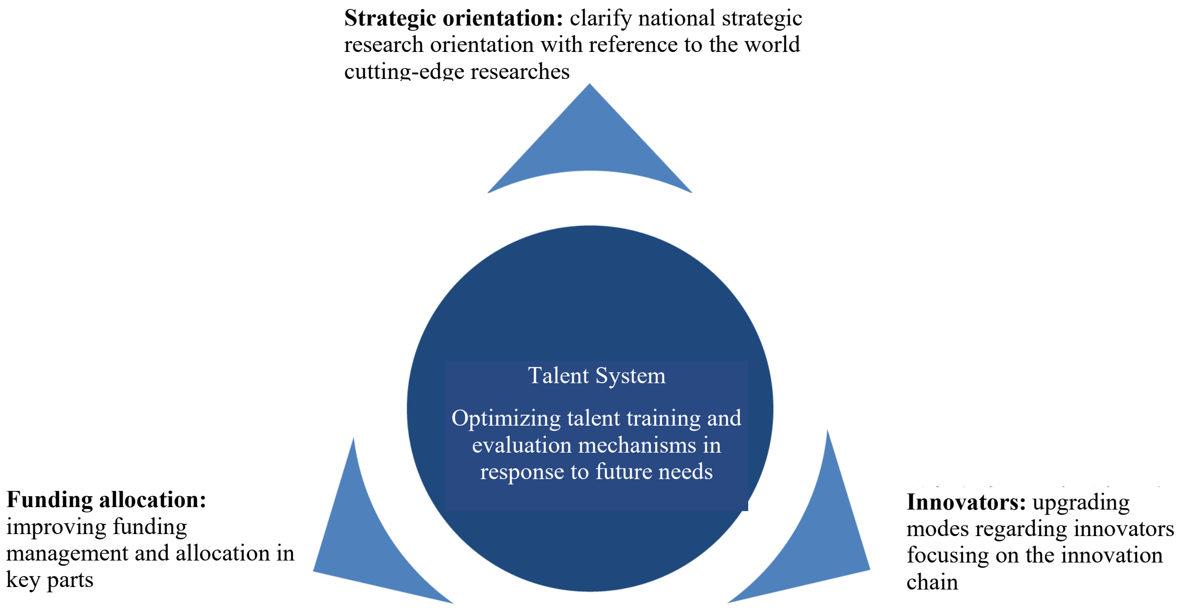
[15] MD-PhD Program Graduates: Current Workplaces, Research Effort, and Types of Research They Do
[16] AMCC National MD-PhD Program Outcome Study

Chapter 4

Future Outlook and Policy Recommendations

In the coming decade, to improve China's basic pharmaceutical research capability, we must centralize on the talent system and optimize talent training and evaluation mechanisms to satisfy future needs for research talents. Meanwhile, we should clarify national strategic research orientation, improve funding management and allocation, and upgrade modes regarding innovators.

Figure 17: With talent system at the center, continuously promote China's basic research to initiate pharmaceutical innovation



Clarify national strategic research orientation with reference to the world cutting-edge research

The government should make clear its strategic orientation to provide guidance for basic research, and highlight strategic areas and forward-looking layouts oriented to international cutting-edge researches and critical national strategic tasks. Looking ahead, China needs to pay close attention to and invest mainly in the following eleven advanced sciences and technologies, which are very likely to become the most active parts and development tendency of global basic biopharmaceutical research.

1. Advanced research technologies / methods

Gene editing improves efficiency of drug R&D. The application of gene editing has significantly shortened the cycle and reduced the costs for drug R&D by increasing efficiency of drug target identification, genetic modification of cell strains and construction of animal models.

Synthetic biology, with artificially designed genetic circuits, genetically engineers human cells or artificial life forms such as bacteria and viruses, which then act indirectly on human body.

These artificial life forms are capable of identifying disease-specific or artificial signals, specifically targeting abnormal cells and lesions, expressing reporter molecules or releasing therapeutic drugs, thus enabling the monitoring of human physiological states, and diagnosis and treatment of typical diseases such as tumors, metabolic diseases, and infections caused by antibiotic-resistant germs.

Stem cells and regenerative medicine provide solutions to the treatment of chronic diseases and organ transplantation. The development of regenerative medicine not only make the treatment of a range of serious or critical chronic diseases possible but bring potential solutions to the shortage of organs for transplantation as well.

Therapeutic vaccine is the latest revolutionary new drug. Following the cytokine gene-modified vaccines and antibodies that emerged successively in modern biopharmaceuticals, a third surge, represented by therapeutic vaccines, is now underway. Therapeutic vaccines have unique advantages over other biological drugs: a) no drug resistance occurs, thus avoiding the emergence of "superbugs"; b) autoimmune is elicited to make diseases such as rheumatoid arthritis and multiple sclerosis curable; and c) vaccines to treat tumors bring new hope to mankind, etc. The innovative drugs targeting these serious or critical illnesses, once commercially available, will turn out to be blockbusters in the market both in the moment and for the future.

The antibody drug industry is gaining momentum. The R&D of antibody drugs has become a research hotspot in the field of biopharmaceuticals, ranking first among all pharmaceutical biotechnology products in recent years. Antibody drugs are not a new type of drugs that appears recently. After decades of technological iterations and upgrades, the monoclonal antibody drugs have ushered in a golden period of rapid use and development, especially the great success reaped in oncology treatment via monoclonal antibody-based immunotherapy. The R&D of next generation antibody drug will target at new indications, new therapeutic targets, new molecules and new therapies.

2. Advanced research fields/subjects

Brain science research findings can be applied to diagnosis and treatment of brain diseases. In the future, with the help of molecular, imaging and related markers, the early diagnosis and intervention of brain diseases will be made easier. Studying on genetic, epigenetic and pathological dysfunctions helps understand the pathogenesis of brain diseases and may make real the cure of commonly occurring brain dysfunctions today. The in-depth understanding of serious or critical brain diseases provides guidance for the development of new drug targets in the prevention and treatment thereof and the development and manufacturing of new drugs.

Human microbiome R&D open up new horizons for healthcare. The cross-innovation driven by integration of basic disciplines with rapidly advancing technologies has overturned the traditional concepts of human body, health and diseases. It provides new visions for addressing the challenges of the aging population, and the detection, treatment and nutritional interventions for serious or critical chronic diseases and cancers. Immunotherapy brings about hope for tumor treatment. The discovery of new tumor antigens/targets and breakthroughs made in key technologies of immune cell design and modification and large-scale cell culture forge strong core competencies for the immunotherapy industry.

3. Advanced research concepts / approaches

Precision medicine promotes efficient diagnosis and treatment of diseases. Based on genes and their epigenetic modifications, structural characteristics of tissue cells, and functional characterization of tissue cells, diseases are accurately diagnosed and even detailed to the types, which then serves as a base for personalized treatment.

Translational medicine is effectively advancing the course of industrial development. With the progress of cross-disciplinary integration, the interdisciplinary collaborative research capability and international competitiveness will be strengthened correspondingly, thus driving the overall development of related disciplines.

The cross-integration and innovation of biotechnology and information technology. The integration of big data in biology and artificial intelligence will have a disruptive impact on industrial development. The development of big biological data has dramatically changed the landscape of life sciences, including industries and fields such as healthcare and drug development. The wave of artificial intelligence represented by deep/machine learning that emerged in recent years has had an overturning impact on scientific research and industrial development in every corner.

Improving funding management and allocation in key parts

1. Optimization of public investment: China's total investment in R&D ranks already the second in the world, of which the total public investment begins to take shape. However, in the long term, to guarantee satisfactory output consistent with the public input, our work shall focus mainly on how to strengthen targeted investment in key parts and allocate funding to projects with great potential in a scientifically equitable manner.

In terms of the amount of investment, as China still lags behind leading countries in the world, we must continue to increase public investment in basic research of pharmaceutical innovation, and strive to accomplish in advance the target of the 14th Five-Year Plan that investment in basic research accounts for more than 8% of R&D investment. In regard to significant national demands and strategic development orientation (such as the aforementioned important sciences and technologies), the government investment needs to be weighted accordingly.

In allocation of investment, we should set up a national biomedical research special fund as what most leading countries was doing, and entrust it to professional management agency for unified management with scientific and fair evaluation mechanism, so as to improve the efficiency of resource allocation. Efforts shall be made to coordinate competitive funding and stable funding to avoid duplicate funding and over-funding. What's more, the competitive and stable funding need to be allocated proportionate to the nature of research institutions and the research fields. For instance, stable funding should be granted to national basic scientific research institutions and national scientific and technological infrastructures of great significance, alongside research fields with strategic, cutting-edge and long-term characteristics. In this way, we will be able to build and maintain high-level research platforms, introduce and retain excellent research talents, and empower these talents to innovate without distraction. In addition, a special funding supporting industrial translation should also be included in the national biomedical research special fund. Where social capital investment is insufficient, it will be used to provide patient capital with high tolerance to facilitate the incubation and translation of basic research findings.

2. **Improving efficiency in the use of funding**: The continued increase in funding for basic research is only one aspect of empowering the source of pharmaceutical innovation; improving efficiency in the use of basic research funding is the other. Universities and research institutions should have well-established funding management organization and system in place, which is

projected to result in a detailed funding management, and make research driven more by achievements rather than investment. The redistribution of stable funding should seek de-administration and be academically oriented so that the disadvantages of rigid management mechanisms, inefficient funding processes and aimless funding orientation are avoided.

Upgrading modes regarding innovators focusing on the innovation chain

1. New mode of scientific research management: In order to stimulate the innovation vitality of universities and research institutions, we need to abandon the talent evaluation mechanism which bases mainly on "four prevails" criteria, and replace it with a diversified and scientific evaluation mechanism. It entails us to break down disciplinary barriers and create an innovation chain that links upstream original discovery and downstream translation and application. We should break the shackles of the traditional system and bring innovator's individual initiative into full play by exploring new modes of scientific research management.

Reforming the evaluation mechanism to set right the “baton” role of assessment criteria. Adjustment for research evaluation mechanisms and management modes should be made to encourage original innovation and translation of basic research findings among universities. To this end, the translation mechanisms and translation results should be considered criteria to include into the evaluation mechanisms of universities and research institutions of certain categories. Through bottom-up driving and motivation approaches, the innovators’ willingness to translate and the efficient application of research findings will become realizable.

Innovation chain should be established to couple & enable universities and research institutions to play due role throughout pharmaceutical innovation. On the basis of the traditional disciplines, new type of R&D institutions featuring cross-disciplinary and cross-functional integration should be established in a bid to promote resource sharing and exchange and cooperation, and function as a bridge that links original innovation in basic research and transfer & translation for industrial application. Efforts should be made to pilot innovative mechanisms and management modes of new type of R&D institutions, to cultivate organizational capabilities of carrying out scientific research and industrialization activities, and thus forge a micro-innovation ecosystem that integrates scientific research, incubation and other functions.

2. Cross-domain collaboration and integration: In terms of exchange between hospital and research institution, as the coordinating body and pilot institution, a national center for advancing translational sciences should be set up to bridge translation from basic medical research to clinical trials via integration and utilization of existing fragmented technologies, resources and facilities. With respect to industry-academia collaboration, more improvement is expected to be made in the industrial translation capabilities of universities and research institutions. The industry is encouraged and provided support to establish third-party trading platforms that have sound and flexible intellectual property trading and market-oriented mechanisms to facilitate technology transfer and industrialization of achievements made by researchers.

Optimizing talent training and evaluation mechanisms in response to future needs

1. More diversified evaluation mechanism: We should, on the one hand, reform the unitary "paper prevails” talent evaluation criterion, and on the other hand, actively strive for a more diversified scientific evaluation mechanism by referring to successful experience abroad, and promote the growth and long-term development of local basic researchers.

Classified evaluation. Customized scientific evaluation dimensions and evaluation methods for professionals working in different fields should be applied in line with the nature of their business, with the focus on real world research and translational value. For talents engaged in basic research, the evaluation should be led by whether they have made novel attempts and substantial contributions to answering vexing scientific questions and pioneering prospective research fields. Also, in consideration of the long period of basic research, we mustn't assess and evaluate talents with short-term quantitative criteria (such as the number of papers published) in a uniform manner. While concerning talents in translational research, the underlined should be whether they have achieved corresponding outputs in breaking through technical bottlenecks and satisfying clinical and national strategic needs. For this purpose, the translation of representative achievements, etc., should be considered in the evaluation of symbolic achievements.

Targeted Peer Review. The review over papers or representative achievements made by the talents should be implemented by a committee consisting of internal and external peer experts in targeted fields to realize "Insider Review". This approach is more likely to be discipline-tailored, avoiding the more general and paper quantity-oriented peer review from a more extensive perspective, and thus emphasizing quality and actual contribution of research itself.

2. Strategies to attracting and retaining overseas talents: Efforts should be made to develop a recruiting platform that provides undated and accurate information for overseas research talents, optimize local research environment and living conditions, and improve implementation of supporting policies after talent introduction. That's how we can attract more leading talents in the fierce international talent market, and how we can successfully recruit, retain and make the best of them and continue to deliver scientific and technological achievements efficiently and with high quality.

Identification and recruitment of talents requires to abandon the "five prevails" criteria that have "seniority prevails" in addition to the aforesaid "four prevails", and to prioritize the needs in the research field and the capability and potential of talents instead.

To start a scientific career and seek growth for talents, the applicability of the "promotion-or-go" rule with time limit for talents of different types and fields needs to be re-evaluated. Also, classified evaluation should be applied to reduce barriers to initiating and accelerating the scientific career of talents (especially young talents) in China. In addition to friendly start-up funding and support measures for scientific research, more convenient and efficient services and guarantees for talents in terms of settlement, residence visa, children's schooling and healthcare should be granted as well.

3. Cultivation of local research teams: The cultivation and retention of local talents play an irreplaceable role in enriching the base and volume of basic research teams and incubating future leading researchers. The existing biomedicine education mode in China is in urgent need of upgrading. If we are to create future-oriented local research teams, we must exert more efforts to comprehensively optimize disciplinary layout, cultivation pathways and teaching philosophy.
Optimizing the layout of talent teams. Basic research is unfeasible without large talent pool. In order to make basic research talents meet the requirements of biopharmaceutical development in China, we should optimize the training modes and pathways for researchers, adjust disciplinary layout with the times, and provide emerging interdisciplinary learning in a timely manner, so as to improve the capability of research teams and keep them informed of cutting-edge sciences and technologies and industrial development.

Cultivation of interdisciplinary talents. Basic scientific research is increasingly driven by intelligence, automation and big data. Hence, we must reinforce our efforts to cultivate composite research and industrial talents with backgrounds in science, medicine, pharmacy and information technology, including improving the education and training modes, clarifying career development plans and introducing inclined supporting policies so that we can capture opportunities in emerging technologies and fill talent gap needed in key links throughout pharmaceutical innovation such as translational research and technology industrial translation. In the second place, breaking down institutional barriers and thus providing channels for the flow of talents among academia, medical community and the industry are also important ways to promote the training and growth of interdisciplinary talents.