From imitator to innovator

The race for new drug research and development is essentially a competition of science and technology policies and systems, according to Song Ruilin, Executive President of China Pharmaceutical Innovation and Research Development Association (PhIRDA).

Research and development of novel drugs demand high investment, a long cycle and high risk. A supportive policy environment with sufficient funding and an effective and comprehensive regulatory system play a crucial role in driving drug research and innovation.

Determined to become a leader in science and technology innovation, China, the world's second-largest pharmaceutical market, has put drug innovation high on its development agenda. The launch of the National Science and Technology Major Project for Drug Innovation in 2008 by the Ministry of Science and Technology demonstrates the government's commitment to this endeavour.

This multi-billion dollar project aims to change the current high dependency on imports of patented drugs and to transform the Chinese pharmaceutical industry from imitating foreign patents to innovating new drugs. Targeting major diseases, the project has supported a series of new projects, including basic research on chemical compounds, pre-clinical pharmacological research and clinical studies. It has also funded the construction of large-scale technology platforms and incubation bases.

Eight years after the launch of the Drug Innovation Major Project, China's basic drug research capabilities have significantly improved, leading to increased publication of quality papers and multiple innovations of new drugs. Comprehensive technology platforms, including Good Clinical Practice (GCP) platforms and Good Laboratories Practice (GLP) platforms underlie an effective research and development system for drug innovation. Chinese pharmaceutical companies are becoming increasingly prominent in new drug discoveries and have successfully launched several first-in-class drug products. These innovative drugs have come to the market on the back of high-quality clinical studies, with many approved for clinical trials abroad, such as in the United States and Japan.

With the support of the Drug Innovation Major Project, a healthy environment for biomedical innovation will ensure China takes a leading position in new drug discovery. ■

Biomedical innovation in China

By **Song Ruilin**, Executive Vice Director, Research Centre of National Drug Policy & Ecosystem, China Pharmaceutical University, Executive President, PhIRDA
Wu Xiaoming, Professor, China Pharmaceutical University
Cheng Yinqi, Deputy Secretary-General, PhIRDA


Song Ruilin

Science and technology are crucial to improve national strength and cohesion. The ever-strengthening link between technological advancement and economic success highlights this fact. Countries worldwide are striving to create national innovation systems to drive science and technology breakthroughs.

Like others, China has realized the urgency in taking effective measures to enhance its scientific and technological strengths and improve independent innovation capabilities. At the end of 2005, the State Council issued a 15-year plan for science and technology development to build an innovative nation. This marked the beginning of the construction of its national innovation system.

The pharmaceutical industry plays a key role for human health, as well as national security and competitive capacity, and therefore, is highly valued by the Chinese government. Launch of the National Science and Technology Major Project for Drug Innovation (Drug Innovation Major Project) represents a strong signal from the central government to encourage industry innovation.

Improvement of government policies encouraging innovation and biomedical development

In light of a sluggish world economy caused by the global financial crisis, China's leaders have, since 2012, implemented a series of comprehensive reforms to address systematic problems that stifle innovation and upset efficient market competition. These range from suggestions for reforming the science and technology systems to measures that promote the innovation capacity of enterprises.

Particularly, in August 2015, a revision of the Law on Promoting the Transformation of Scientific and Technological Achievements for the first time gave research institutions disposal rights of their research results. New regulations allowed researchers or teams from state-owned research institutions and universities to retain at least 50% of the transfer or license fees, breaking institutional barriers to technology transfer.

Released in mid-2016, Outline of the National Strategy of Innovation-Driven Development further clarifies the need for transformation, such as in development patterns, innovation capabilities and resource allocation. These major policies provide guidance for China to promote coordinated reforms of administration, science and economic systems. They will allow for market incorporation of innovation, and healthy and sustainable economic development.

As the biopharmaceutical industry is becoming a major economic driver in the new wave of science and technology revolution, the Chinese government has released a series of policies to boost biomedical development. In 2009, China proposed making the bio-industry a pillar for high-tech development and an industry of strategic importance. This was reinforced by the National Medium- and Long-term Plan for Major R&D Infrastructure Construction (2012-2030). This plan ratified support for infrastructure construction for modern translational medicine research, frontier life sciences research and other basic research. The Healthy China 2030 plan issued in 2016 explicitly proposed a focus on the pharmaceutical sector to boost the health industry. Moreover,

the 13th national five-year plan, approved in December 2016, called for promoting biomedical innovation by accelerating the approval and launch procedures of innovative and urgently-needed drugs, while supporting the production of low-priced drugs, orphan drugs and paediatric drugs. These responsive policies have highlighted the irreplaceable role of the pharmaceutical industry in national policy and economy, and its significance in China's endeavours for innovation breakthroughs and a global advantage.

Guided by the national policy, the China Food and Drug Administration (CFDA) has reformed drug review and approval mechanisms to improve efficiency. It has piloted priority review and a mechanism that makes a market authorization holder liable for the entire drug development process, redistributing the liabilities for the pharmaceutical industry. Meanwhile, the drug list for the national basic medical insurance is under revision, in an attempt to include more urgently needed drugs and to initiate a price negotiation mechanism for inclusion of innovative drugs.

Pharmaceutical innovation led by the Drug Innovation Major Project

Spanning 2008 to 2020, the Drug Innovation Major Project is set to promote research and development (R&D) of innovative drugs as well as overall innovation capabilities. Implementation is divided into three stages: the innovation-oriented transformation period in 2008-2010, the rapid growth period in 2011-2015 and the leapfrog development period in 2016-2020.

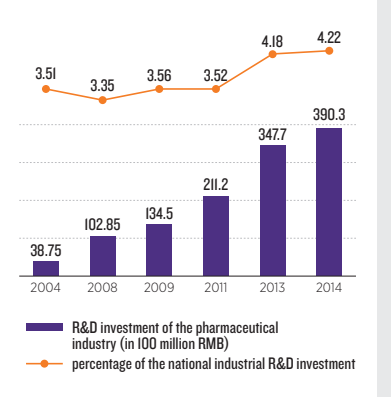
Since 2008, China has invested 12.8 billion RMB to support building key platforms for R&D of innovative drugs and to accelerate the transformation from imitation to innovation. By easing technology bottlenecks, the Drug Innovation Major Project has significantly boosted China's drug R&D capabilities, with a series of innovative pharmaceutical enterprises and new drug products emerging.

R&D investment on the rise

According to the Organisation for Economic Co-operation and Development (OECD) data, China's R&D intensity has been increasing since 2008 and reached more than 2% of GDP after 2013, surpassing that of the European Union (EU). Domestic statistics suggest that China's R&D investment totalled 1.4 trillion RMB in 2015, with an R&D intensity of 2.1% of GDP. A national survey of all enterprises in 2014 showed that 41.3% of enterprises are engaged in innovation activities.

The pharmaceutical industry has been especially active in innovation, continuously increasing R&D investment. The proportion of R&D investment from the pharmaceutical industry climbed from around 3.49% of total R&D investment by all industries before 2011 to 4.2% on average in 2013-2014. The average growth rate of the R&D investment by the pharmaceutical industry reached 41.17% from 2008 to 2014. The pharmaceutical industry's average R&D intensity remained higher than the national average from 2004 to 2014, leading the latter by over 0.8 percentage points in 2013-2014.

R&D investment of the Chinese pharmaceutical industry as a percentage of national industrial R&D investment



Key pharmaceutical enterprises stand out: Hengrui Medicine invested 3.78 billion RMB in R&D from 2008 to 2015. It ranked first among its Chinese peers in 2015 with a total R&D investment of 892 million RMB, and R&D intensity reaching 9.57%. Chia Tai Tianqing's R&D intensity was higher than 10% in both 2014 and 2015, exceeding those of Bayer and Gilead in 2015.

Outstanding patents and publications

The large number of drug patents earned by key research institutes and innovative pharmaceutical enterprises demonstrates China's rapidly improving innovation capabilities. The growing number of international patents gained by Chinese enterprises particularly shows their increasing global competitiveness.

Chinese pharmaceutical companies are also publishing more highly cited papers in high-quality journals, evidence of their strong research competence.

Burgeoning new drug products and an innovative industry

With an emphasis on clinical application, the Drug Innovation Major Project has boosted the invention of innovative and first-time generic drugs, leading to products such as icotinib, chidamide and entecavir. Their fast entry to the market helps address unmet clinical needs and ensures drug availability.

Comprehensive support to the whole chain of new drug R&D has strengthened original innovation capabilities of research institutions and enterprises. A race to create "me-too" drugs has shifted to a competition to create "me-better" drugs by tracking new global drug targets. This has brought a growing number of drugs with new targets and action mechanisms, as well as antibody coupling drugs and immunotherapy drugs for tumours, such as PD-1 and PD-L1. CFDA statistics shows that the number of class 1.1 and new class 1 chemical drugs

received for evaluation has increased by 4.6 times from 2008 to 2016.

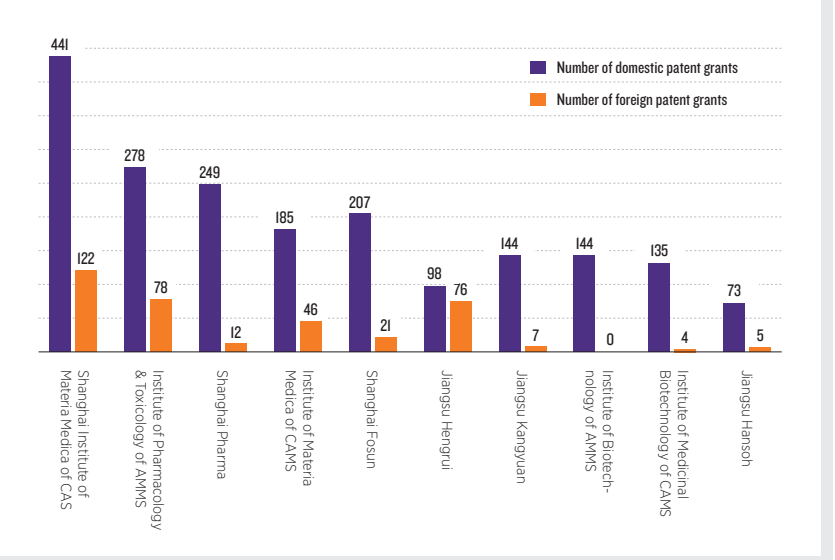
Many innovative drugs supported by the Drug Innovation Major Project are approved for clinical trials in the United States or Europe, such as several -tinib products developed by Hutchison Whampoa; the recombinant humanized PD-L1 single-domain antibody developed by Suzhou's Alphamab; and chidamide. Conbercept was even approved to directly conduct phase III clinical trial in the United States.

Encouraged by supportive policies, many biomedical experts are returning to China to start businesses. This has sparked the enthusiasm of pharmaceutical enterprises, motivating them to innovate. As a result of this brain boomerang, international cooperation is also burgeoning and drug production is becoming increasingly global. Several innovative pharmaceutical enterprises have transferred licenses of their patented antibody products overseas, receiving transfer payments amounting to billions of dollars.

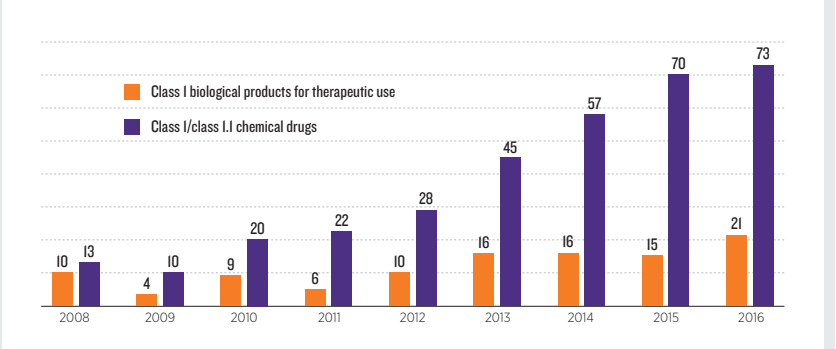
Capital funds financed by Chinese enterprises also hit new highs. Innovent Biologics and CStone Pharmaceuticals financed $260 million and $150 million dollars respectively in 2016, ranking second and sixth in GEN's 2016 wealth list of top 10 young companies. Moreover, BeiGene, as the first Chinese pharmaceutical company to launch an IPO in the United States, was listed on NASDAQ in 2016 and raised $158 million.

The production scale of Chinese pharmaceutical industry is growing steadily due to industrial optimization and upgrades, with rising revenue and profitability. Despite the weak global economy and the domestic limit on drug purchasing prices, the average growth rate from 2010 to 2015 of main business profits in the pharmaceutical industry was about 9 times higher than that of the national industrial sectors.

Domestic and foreign drug patent grants received by key Chinese institutions, 2006-2015



Processed applications for class 1 new drugs by the Chinese Centre for Drug Evaluation, 2008-2016

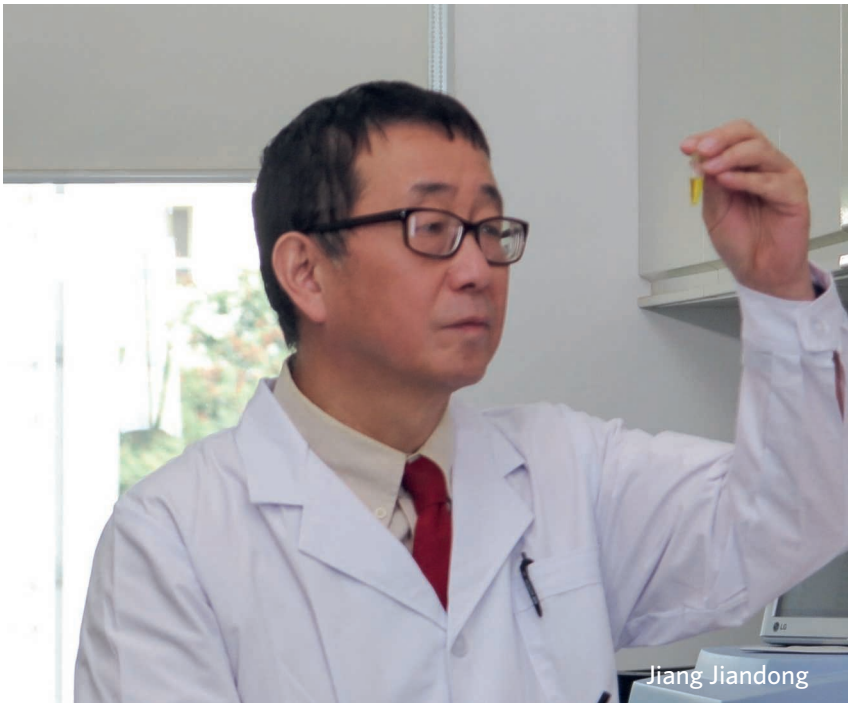


The Drug Innovation Major Project has been instrumental in promoting pharmaceutical innovation and sustainable development of the industry. It will continue supporting development of major drugs, relevant key technologies, and drug innovation systems in the following five years.

Despite major inroads, R&D investment and output efficiency of the Chinese pharmaceutical industry remain relatively low when compared with other technologically advanced countries; while new drugs under research are concentrated in a narrow band, limiting breakthroughs in first-in-class drugs. Supportive policies to guide and motivate further innovation are still needed. The state government needs to urgently form consistent policies via top design and systematic optimization to create a healthy biomedical ecosystem.

Enhanced innovation and development of the Chinese pharmaceutical industry will contribute significantly to China's economic reform, facilitating stable growth and bringing social benefits. It will also provide the impetus for China to march towards an innovative future. ■

Hitting targets in basic drug research



By **Jiang Jiandong**, Director, Institute of Materia Medica, Chinese Academy of Medical Sciences
Wang Min, Director, Research Department, PhIRDA

Pharmaceutical research demands the application of advanced technologies from across the fields of medicine, chemistry, biology, mathematics and others. Recognizing its importance, the Chinese government has put great stock in basic drug research, with major funding support underlined by a National Science and Technology Major Project for Drug Innovation (Drug Innovation Major Project) and by the National Natural Science Foundation of China (NSFC). Having shifted their focus from generic drugs to innovative ones originated from China, key Chinese universities and research institutions have achieved remarkable progress in basic pharmaceutical research since 2000, particularly in drug targets, natural products and pharmaceutical biotechnology.

Progress in drug target discoveries

Gram-negative bacterial infection is highly prevalent worldwide and presents as a major challenge, given growing drug-resistance to many antibiotics. In search of new antimicrobial drug targets, researchers from the Institute of Biophysics at the Chinese Academy of Sciences (CAS) have concentrated on lipopolysaccharides (LPS), the main component of the bacteria's protective outer membrane. The last stage in the biosynthesis of LPS is the formation of a membrane protein complex, the LptD-LptE, which is responsible for moving LPS into the external leaflet of the outer membrane. Using high-resolution crystal structure analysis, the team identified the potential of the two-protein LptD-LptE complex as a drug target, due to its architecture, which researchers describe as plug-and-barrel. The finding sheds light on new antibiotic strategies against gram-negative bacteria.

Drug-resistance to antimicrobials is also a major cause of increased mortality from tuberculosis (TB). A group of researchers from the Institute of Medicinal Biotechnology at the Chinese Academy of Medical Sciences (CAMS) sought new anti-TB drugs and found a novel drug target in the interactions between two TB bacteria's ribosomal proteins, L12 and L10. Using a yeast two-hybrid system for high throughput screening, they obtained multiple inhibitors of L12-L10 interaction, which have become lead compounds for a new generation of anti-TB drugs.

Chinese scientists are also enhancing research on structural biology to guide drug design. Researchers from the Shanghai Institute of Materia Medica (SIMM) at CAS have analysed crystal structures of several major G protein–coupled receptors (GPCRs), which are popular targets of many modern drugs. They disclosed the mechanism of serotonin receptor-ligand interactions and specific signal transduction pathways, providing structural basis for designing serotonergic drugs. Chemokine receptor, CCR5, is a key player for HIV entry. SIMM researchers' analysis of the crystal structure of CCR5 in complex with maraviroc, an anti-HIV drug, revealed maraviroc's mode of action of allosteric regulation and provided detailed insight on drug mechanism for the anti-HIV drug. Moreover, their findings on the mechanism of interactions

between purinergic receptors and other drug molecules contributed to the development of new antithrombotic drugs. The study on three-dimensional structure of the rhodopsin-arrestin complex revealed arrestin interactions with GPCRs, which guided studies on signal transduction pathways of GPCRs and GPCR desensitization. Internationally recognized, these discoveries in the GPCR field have significantly promoted drug research and development (R&D) for migraine, HIV/AIDS and cardiovascular diseases.

Research on ion channels is a key area supported by the Drug Innovation Major Project. Researchers from the School of Life Sciences, Tsinghua University have been focusing on the excitation–contraction coupling of skeletal and cardiac muscles, a process controlled by a series of proteins. The voltage-gated calcium (Cav) channels on muscle cell membranes and ryanodine receptors (RyRs) in the sarcoplasmic reticulum membrane, in particular, play an essential role in this process. Malfunction of the Cav channels will lead to diseases such as arrhythmia and epilepsy; while mutations of RyRs are associated with the central core disease and malignant hyperpyrexia. Seeing the potential of Cav channels for drug targets, Tsinghua researchers have studied structures of these membrane proteins and provided insight into innovative optimization. Published in top academic journals, their results have attracted strong attention from international peers.

Another focus of the Drug Innovation Major Project is anti-diabetes signal pathways. Scientists from the Institute of Materia Medica (IMM), CAMS, proposed that Galectin-3 (Gal3), a protein in the lectin family, can mediate insulin resistance. Gal3, mainly secreted by macrophages, is found elevated in both obese humans and mice. It leads to insulin resistance and glucose intolerance when administered to mice, while its inhibition, either through genetic or pharmacologic means, improves insulin sensitivity in obese mice. More importantly, the research team found that Gal3 can directly bind to insulin receptors and inhibit their downstream signalling. The discoveries illuminate a new role for Gal3 in insulin resistance of hepatic, muscle and fat cells, underlining Gal3 as a key link between inflammation and decreased insulin sensitivity. Inhibition of Gal3 offers new potential for treating insulin resistance.

New efforts in natural products

Natural products have a long tradition in Chinese medicine and characterize China's drug innovation. The Nobel Prize winning discovery of artemisinin, an anti-malaria drug, is such an example. While previous research in the field has mainly been on phytochemistry, new biotechnologies and theories have largely promoted our understanding of drugs from natural products.

" Natural products have a long tradition in Chinese medicine and characterize China's drug innovation. "

One example is the discovery of arsenic's clinical value in leukaemia treatment by scientists from the Ruijin Hospital, affiliated with Shanghai Jiaotong University, and Harbin Medical University. Having been used in traditional Chinese medicine for thousands of years, arsenic was recently found to have clinical effectiveness in treating acute promyelocytic leukaemia (APL), which has garnered worldwide attention. Arsenic trioxide (As_2O_3) works by promoting degradation of an oncogenic protein, a process triggered by a regulatory protein modification. Researchers from the Ruijin Hospital further revealed how As_2O_3 induces this post-translational modification and identified the direct target of As_2O_3. Their work showed that differentiation induction by As_2O_3 is a highly effective mechanism for APL treatment.

Researchers from CAMS' Institute of Medicinal Biotechnology, in collaboration with physicians from the First Hospital of Nanjing, found the potential of berberine to lower blood lipids. Berberine is a botanic compound present in a variety of herbs and is a popular non-prescription drug in China for treating bacteria-caused diarrhoea. On hepatic cells, it stabilizes the mRNA of low-density lipoprotein receptor (LDLR) and elevates LDLR expression through activating ERK signalling path, and thus, efficiently lowers blood cholesterol. This mechanism has been confirmed in animal experiments, as well as in humans. Oral administration of berberine for three months in patients with hyperlipidaemia showed significantly lowered levels of cholesterol, triglyceride and LDL, with no obvious side effects. The stable effectiveness and novel mechanism of berberine provide a clinical edge over cholesterol-lowering statin drugs. Berberine research, supported by the Drug Innovation Major Project and NSFC, has gained international recognition for its widely approved lipid-lowering effects.

Natural compounds also have potential use in stem cell regulation, according to researchers from the College of Life Sciences, Peking University. The possibility to induce pluripotent stem cells from somatic cells provides rich cell resources for medical research, including regenerative medicine, studies of disease mechanisms and drug discoveries. However, technical challenges in genetic manipulation and strategies limit their clinical applications. Using a combination of seven small-molecule compounds, several of which are natural compounds, the team generated pluripotent stem cells from mouse somatic cells.

The induced stem cells are similar

to embryonic stem cells either in gene expression profiles, epigenetic status, differentiation potential, or germline transmission. This chemical reprogramming strategy presents great potential value as a new approach for generating functional cell types for clinical use.

Biotechnology in pharmaceutical research

Successful generation of live replication-incompetent virus vaccines by researchers from the School of Pharmaceutical Sciences, Peking University in 2016 might mark a revolutionary progress in vaccine research. The new type of vaccine, created by expanding the genetic code of the influenza A virus genome, presented superior immunogenicity and immune protection effects over conventional flu vaccines. The core theory underlying this study is the creation of one or more premature termination codons (PTCs) by mutating genes responsible for viral replication. Unable to replicate, viruses with PTCs become vaccines that will not cause diseases. More importantly, this live viral vaccine can turn wild-type viruses into PTC-containing viruses, weakening, or even eliminating the ability of wild-type viruses to replicate. Thus, the vaccine might represent a new therapeutic approach for viral diseases.

The biosynthesis of natural products is a hot topic in synthetic biology. Small-molecule thiols, a class of organic compounds widespread in eukaryotic and prokaryotic systems, are typically known for their protective role against redox imbalance in cells caused by various endogenous and exogenous factors. Scientists from Shanghai Institute of Organic Chemistry, CAS, found that the coupling of two small-molecule thiols plays an essential role in the biosynthesis of lincomycin A, a sulphur-containing antibiotic that has been widely used for half a century in the treatment of gram-positive bacterial infection. The finding offers evidence of thiols' role in assemblies of functional molecules. It also provides a scientific basis for applying synthetic biology approaches to scale up production of the lincomycin antibiotic and to promote assembly of active sugar-containing drug molecules. The research team has also identified two enzymes that catalyse the cascade Diels-Alder reaction in nature, providing new strategies for applying biosynthetic approaches to produce molecules with cyclic rigid scaffolds for drugs.

With support from the Drug Innovation Major Project, a team from CAMS' IMM, focusing on compounds extracted from rare plants, has used synthetic biology technologies to achieve sustainability of such resources. From *Aspergillus terreus*, a fungus typically found in soil, they have found a new enzyme of the aromatic prenyltransferase family, AtaPT, which can add hydrophobic groups to various aromatic compounds in a process known as prenylation. Based on this, the team incorporated site-directed mutagenesis technology to change the promiscuity of AtaPT and control product prenylations. The finding sheds light on producing new structurally diverse prenylated derivatives for drug discovery. Another team of the same institute has identified a way to obtain new resources for drug discovery. They used epigenetic genome modification to activate silent gene clusters in fungi, which offer rich biosynthetic potential for natural products.

Biotechnology has also been used for the gene identification of medicinal herbs at the Institute of Medicinal Plant Development (IMPLAD), CAMS. IMPLAD researchers have proposed, for the first time internationally, using internal transcribed spacer 2 (ITS2), a nuclear genome sequence, as the universal DNA barcode for plant identification. By analysing and comparing seven DNA barcode candidates in more than 6,600 medicinal herbs, of 4,800 species, 753 genera, 193 families and seven divisions, they have built up "gene identity" for medicinal plants using ITS2. The work has led to the world's largest DNA barcode database for identification of medicinal plants and gained worldwide attention. IMPLAD's plant barcoding technology has also opened a new avenue for identification of traditional Chinese herbal medicine.

Furthermore, impressive progresses are seen in medicinal chemistry and analysis of herbal regimens using modern technologies.

Continuous support from national funds has led to significant progress in China's basic pharmaceutical research, which no longer just follows western trends, but is also leading original innovation. Major research institutes and universities have created an environment that encourages original research. The above review enables a better understanding of the status quo in China and will benefit planning of basic drug research, which is expected to be in full bloom soon. ■

New horizon: Drug trial system proves value of home-grown breakthroughs

By **Shi Yuankai**, Deputy Director, National Cancer Centre/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Feng Lan, Secretary-General, PhIRDA

China has made great strides in new drug development in the last 20 years, thanks to a national overhaul of the drug research and development (R&D) landscape, underpinned by financial support for R&D and clinical studies. Technological systems in line with international standards have been formed for clinical evaluation of new drugs and a growing number of innovative drugs are now undergoing clinical trials. As a result of these improvements, China's significant new drug R&D breakthroughs are gaining international recognition.

Introduction of the concept of good clinical practice (GCP) into China in the 1990s led to the establishment of a network of GCP clinical trial centres and ethics committees. The government put clinical study at the forefront and launched a project to develop, from 1996 to 2000, 10 patented class 1 innovative drugs and construct five drug safety evaluation centres, five clinical trial centres and five new drug screening centres that met world standards. Support for new drug R&D was kept up for the following five years. Then, from 2006 to 2015, under the National Science and Technology Major Project for Drug Innovation, a national system for new drug clinical evaluation came into shape.

China's drug R&D is transforming from imitation of products to original innovation. An increasing number of drugs created in China are being approved for clinical trials and many significant results are being published in international academic journals. These achievements indicate China's increased clinical study strengths. Major drug R&D breakthroughs also shed light on development trends of China's clinical study.

High efficacy and safety of China-originated drugs

Lung cancer is a leading cause of cancer deaths in China. More than 80% of cases are non-small cell lung cancer (NSCLC) and around 70% of the patients are already at an advanced stage when diagnosed, which limits treatment options. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is a most cutting-edge treatment option for advanced NSCLC in the decade.

Icotinib hydrochloride tablet, developed by Betta Pharmaceuticals Co., Ltd., is China's first and the world's third EGFR-TKI product to hit the market. Direct comparison in clinical trials with gefitinib, the first EGFR inhibitor, showed that icotinib had similar efficacy and fewer side-effects. In this world's first head-to-head comparison between two EGFR-TKIs in 399 NSCLC patients under the second or third line treatment (ICOGEN study), icotinib has a non-inferior progression free survival (PFS) compared with gefitinib (4.6 vs 3.4 months, p=0.13) and lower incidences of overall adverse event (AE) and diarrhoea. With robust study design, the results were widely recognized by the

international community, demonstrating China's important contribution to drug innovation and its enhanced clinical study capability.

Breakthrough in vaccines targeting major infectious diseases

Clinical trials on vaccines targeting hand, foot, and mouth disease (HFMD) and poliomyelitis, both major infectious diseases threatening the health of infants and children worldwide, displayed China's improved capability in vaccine R&D and clinical study.

HFMD is primarily caused by enterovirus 71 (EV71). Targeting this virus, Institute of Medical Biology, Chinese Academy of Medical Sciences (CAMS) developed an EV71 inactivated vaccine and conducted a randomized, double-blind, placebo-controlled phase III clinical trial. Results showed 100% EV71 antibody positive conversion rate, with no serious AE, suggesting high potency. Based on this result, China Food and Drug Administration (CFDA) approved the EV71 vaccine to go on market in 2015, making it the world's first approved EV71 inactivated vaccine.

CAMS Institute of Medical Biology also developed an inactivated polio vaccine made from sabin strains (vero cells). Their clinical trial showed that the vaccine presented good tolerance and had a comparable antibody positive conversion rate and an antibody level to that of the attenuated oral poliomyelitis vaccine (OPV) and an inactivated poliomyelitis vaccine (IPV) produced from wild-type poliovirus strains. The results led to CFDA approval for initial worldwide marketing of the vaccine in 2015.

Big-data-assisted clinical research

Clinical study based on the Chinese population is urgently needed to guide national drug development and treatment. The China Stroke Primary Prevention Trial (CSPPT) is a study which explored the effect of enalapril maleate and folic acid tablets on the occurrence of first stroke among people with hypertension. The rationale of the study is based on a meta-analysis published in 2007, which suggested that folic acid supplementation reduced the risk of stroke by 18%. Specifically, when folic acid was used in first-level prevention, the risk of stroke was reduced by 25%; and when supplemented with folic acid for three years or more, the risk could be reduced by 29%. Based on the evidence from this meta-analysis, the CSPPT was designed as a randomized double-blind trial with 20,702 patients of hypertension, who were randomly divided into two groups — one receiving enalapril maleate and folic acid tablets, a combination of enalapril, an antihypertensive drug, and folic acid, while the other receiving enalapril alone. The combination of enalapril and folic acid had a relative risk reduction of 21% for first stroke among hypertension patients. Meanwhile, it significantly reduced the risk of ischemic stroke by 24% and other cardiac events by 20%. The effect was even better in those with H-type hypertension (with elevated plasma homocysteine level).

The right response

Single-arm clinical trials, relying on external historical data for comparison, are typically used for drug efficacy and safety evaluation. With simpler design and shorter study periods, they are preferred for R&D of new drugs for rare diseases.

The clinical trial of chidamide adopted the single-arm multi-centre design to explore the objective response rate (ORR) in 79 patients and showed an ORR of 28%. A safety study of 195 patients reported no unexpected AE. The main AE was haematological toxicity, while blood clots, prolonged QT interval on electrocardiograms and pericardial effusion (too much fluid around the heart) often reported in similar drugs are rarely seen.

The rigorous design and analysis made the CSPPT study recognized globally. Guided by the theory of epidemiology, the CSPPT conducted multi-centre collaboration with grass-roots hospitals to expand its coverage population. Using meta-analysis based on big data, the clinical research captures Chinese population characteristics and is conducive to developing innovative drugs more suitable for domestic populations. Such study avenues also meet research needs for precision medicine.

An offshoot of the CSPPT is focusing on the comparative effect of Enalapril Maleate and Folic Acid Tablets on the prevention and control of H-type hypertension. The clinical study is underway in more than 1,800 hospitals country-wide, using the combination tablets to treat H-type hypertension.

Improvement in drug R&D for rare diseases

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of rare and aggressive non-Hodgkin's lymphoma (NHL) with poor clinical outcome. PTCL represents about 25%-30% of NHLs in China. With no standard therapy, its median overall survival (OS) is about two years and the five-year OS is only about 26%.

Chidamide tablet, developed by Shenzhen Chipscreen Biosciences Ltd., is a highly-selective histone deacetylase (HDAC) inhibitor and the world's first oral HDAC inhibitor for treating PTCL. By inhibiting certain HDAC sub-types, chidamide triggers chromatin remodelling and changes gene expression in multiple signal pathways to achieve anti-tumour effect. In clinical trials, it showed promising therapeutic effect and less toxicity compared with similar PTCL drugs approved by US Food and Drug Administration (FDA). Chidamide was approved for sale by CFDA in 2014. Its successful launch suggests that new drug R&D for rare diseases is possible with clinical trials spanning a relatively short period.

© jxfzsy/Getty

© Jason Butcher/Getty

Growing clinical study on drugs for common diseases

Gastric cancer is the third leading cause of cancer deaths in China and nearly half of the world's gastric cancer patients are from China. However, there is no standard therapeutic regimen for advanced stage patients after the failure of second-line treatment.

Apatinib mesylate tablet, developed by Jiangsu Hengrui Medicine Co., Ltd., is a small-molecule inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2) used for the treatment of advanced gastric cancer. By blocking the downstream signal transduction, it inhibits tyrosine kinase formation and tumour neovascularization to treat cancer. A phase III placebo-controlled clinical trial with 273 patients showed significantly longer OS and PFS for the apatinib group compared with the placebo control group. Apatinib also showed good tolerability and no uncontrolled AE. It was approved for market by CFDA in 2014. Many innovative drugs for other common diseases are undergoing clinical study in China.

Increasing approval by US FDA

Age-related macular degeneration is a leading cause of severe vision loss in the elderly. Conbercept ophthalmic injection, a recombinant fusion protein, is an anti-vascular endothelial growth factor drug developed by Chengdu Kanghong Pharmaceutical Group Co., Ltd. Its phase II clinical trial suggested improvement in vision with three months of continuous injection. Regular or need-based injection of conbercept in the following year would continue vision improvement and proved safe.

Conbercept has gained approval for phase III clinical trial in the United States, making the prospect of hitting the American market a possibility. This marks an international recognition of the robust design, quality control and operation processes of Chinese clinical trials.

Prospect of Chinese clinical study

CFDA enacted the drug clinical trial management regulation in 1998. Since then, China has seen continued improvement in clinical trial-related laws and regulations. From 1996 to 2015, through the sustained government support, and unremitting efforts of all parties to build national clinical trial platforms, a strong technical system for clinical evaluation of new drugs has been created in China. Reliable clinical trials require strong laws and regulations, high-quality facilities and clinical investigators, and multi-party collaborations. With the increasing number of new drugs in China, demands for clinical trials are increasing and expectations are rising. We are looking forward to seeing more Chinese innovative drugs emerging on the back of high-quality clinical studies. ■

Blueprint for success R&D a top priority

By **Jiang Hualiang**, Director, Shanghai Institute of Materia Medica, Chinese Academy of Sciences
Wang Yuanyuan, Deputy Director, Information Department, PhIRDA


Jiang Hualiang

Building an effective new research and development (R&D) system for pharmaceuticals is fundamental to China's drug innovation and is an objective in the National Science and Technology Major Project for Drug Innovation (Drug Innovation Major Project). A new system is considered essential to improving the country's pharmaceutical research competency.

In the execution plan of the project, a blueprint made up of specialized technology unit platforms for pre-clinical and clinical research is described. The pillars of the system are national large-scale, comprehensive technological platforms and enterprise-led new drug incubators.

Drug Innovation Major Project in action

Since the implementation of the Drug Innovation Major Project in 2008, large, comprehensive platforms, technology unit platforms and resource platforms have been improving. Integration of new drug R&D and industrial chains has led to the formation of a connected, standardized innovation system that covers drug target identification and verification, drug invention, and systematic pre-clinical and clinical trials. This network has linked academic innovation — led by research institutions and universities — with technological innovation steered by pharmaceutical enterprises, improving the country's overall new drug R&D capacity.

National-level comprehensive platforms

Universities and institutions with strong innovation abilities are selected to lead the construction of large, comprehensive research platforms targeting major diseases. Leveraging their own expertise and regional resources and teaming up with pharmaceutical companies and hospitals, they have built systems that cover new drug identification, druggability evaluation, industrialization and clinical application/translation. These systems have made a significant positive impact on China's scientific capacity for drug innovation.

Represented by the Chinese Academy of Medical Sciences (CAMS), Shanghai Institute of Materia Medica (SIMM) of the Chinese Academy of Sciences (CAS), China Academy of Chinese Medical Sciences (CACMS), Sichuan University, Academy of Military Medical Sciences (AMMS) and the Fourth Military Medical University, large and comprehensive platforms are providing high-quality R&D services to drive drug development.

CAMS has formed a new drug R&D chain, covering the entire process from target identification to pre-clinical evaluation. It has passed phase III clinical trials and applied for production licenses for three new drugs. Its 84 technology transfer contracts from 2011 to 2015 demonstrate its success in clinical translation, based on better fundamental research, indicated by the publication of an average of 400 SCI papers annually.

Focusing on small-molecular-targeted drugs, **SIMM** has built a comprehensive platform of new drug R&D that meets international standards, offering multiple

	New drug certificates	Drugs in clinical trials	Drugs in pre-clinical	Drug candidates in pipeline	Technical service contracts
CAMS	3	16	26	30	1049
SIMM	1	14	22	40+	935
Sichuan University	3	11	N/A	N/A	852
AMMS	3	9	N/A	30	N/A

Achievements since the 12th five-year plan for selected institutions

functions, advanced technologies and efficient operations. Since 2011, it has completed 141 pre-clinical evaluations for class-1 new drugs and 28 technology transfer projects.

CACMS has built a cutting-edge technology platform for traditional Chinese medicine (TCM), making technological breakthroughs in medicine for injection and inhalation, composition design for Chinese herbal compounds, evidence-based evaluation of TCM and secondary development of TCM. Currently, 42 new drugs are in development and five new drug certificates have been obtained, including for an anti-inflammatory ointment, a capsule for the treatment of diabetes and kidney problems and granule to ease fever. CACMS's creation of new technologies and a model for secondary development of TCM won it first prize in the National Science and Technology Progress Award.

Sichuan University is devoted to building and improving a highly-integrated technology platform for new drug development. It took bold steps in several pilot production process technologies, such as for recombinant proteins or viruses, plasmid DNA, isolation, purification and synthesis for small molecule drugs and targeted PEI. Besides new drugs currently in clinical trials, it has one new drug recently submitted for clinical trial application.

Drugs for the prevention and control of serious public health threats, such as flu pandemic, super bacteria, Ebola and cyanide poisoning are the focus of the **AMMS**, which is dedicated to building a public health emergency security system. Between 2011 and 2015, it obtained 10 approvals for new drug clinical trials with another four applications filed for clinical trials. It has won national awards for science and technology progress and for technology innovation.

The Fourth Military Medical University applies biotechnology to drug R&D. It has established phage antibody libraries, including one for liver cancer, and a protein bioinformatics research platform. It has harnessed structural biology techniques and key technologies for cell and gene therapy, and for tissue engineering products. Its establishment of a polypeptide and protein drug preparation system and a drug quality control system based on biotechnology enables large-scale preparation of biological products.

Unit technology platforms

To improve the R&D chain for drug development, the Drug Innovation Major Project has supported selected unit platforms of specialized technologies, which has seen significant standardization of practice and enhancement of overall technical capabilities for new drug R&D.

For example, several Good Clinical Practice (GCP) platforms have managed or taken part in international multi-centre new drug clinical trials, demonstrating that Chinese new drug clinical research is in line with international practices. Meanwhile, several Good Laboratory Practice (GLP) platforms are internationally accredited, and have conducted drug safety evaluations for international pharmaceutical companies.

Specifically, the GLP platforms have passed 19 international accreditations, including those from the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), OECD, US FDA, the ANSI-ASQ National Accreditation Board (ANAB) and the United Kingdom Accreditation Service (UKAS). As of August 2016, of all 13 GLP platforms supported by the Drug Innovation Major Project, 11 have been AAALAC accredited and four certified by OECD's GLP. Significant improvements in the platforms' service capabilities were demonstrated by the 4,319 drug safety evaluations conducted and 72 clinical trial licenses that they have helped to gain.

Supported by the Drug Innovation Major Project, the Chinese National Compound Library is a national drug discovery resource platform. It is centrally managed with standardized

quality control and optimum storage conditions. It was collaboratively built by the National Centre for Drug Screening and seven institutions across China. By the end of 2016, the core library had more than 1.8 million compounds stored; the largest public compound library in Asia, possibly the world. It has provided 183,700 samples to 83 research projects.

The library's online resource network has made more than 1.27 million compound structures accessible. Its 1,120 registered users can search for compound structures and screening models, and apply for screening services online. By providing sample resources, activity screening and technical support, the network offers a full range of services to research institutions, universities and pharmaceutical enterprises.

Industry technology platforms

Stimulating the biomedical industry by improving enterprises' technological capacity is among the Drug Innovation Major Project's objectives. To this end, a series of new drug incubators, biomedical industrial parks and industry-university-research partnerships have been built, leading to regional biomedical industry clusters and a blooming innovation system for enterprises.

Thanks to industry-university cooperation, new drug incubators have harnessed independent science and technology innovation, research translation and market competition and formed a scientific development pattern. With the establishment of a complete chain that links innovation, drug R&D and industrialization, pharmaceutical enterprises have achieved substantial progress in drug pilot production and technology reformation.

For example, Ascentage Pharma has opened its technology platform for R&D of original small-molecular-targeted anti-tumour drugs. It has provided drug design and development services for multiple class 1.1 original drugs to other enterprises around the country by sharing its hardware, value-added techniques and other technology sharing services.

The future

With the support of the nation's 13th Five-Year Plan, the Drug Innovation Major Project hopes to push China's drug innovation technology and GCP platforms to a global level and promote service capabilities of key resource platforms.

Under this ambition, it aims to improve innovation systems for new drug R&D in immunotherapy, gene therapy and nucleic acid drugs, antibodies and bio-macromolecular drugs, new TCM genres, emergency medicine, small-molecular-targeted drugs and natural product drugs. These would provide technical support to China's growing biomedical industry by significantly improving drug innovation and service capabilities.

Meanwhile, it will promote the standardization and professionalism of GCP platforms by training professional principal investigators, doctors and nurses for clinical research and capitalizing existing contract research organization resources.

And finally, it will expand the storage capacity of compound libraries, related TCM libraries and sample libraries to improve support for drug R&D. The resource platforms will have greater technology sharing capacity and provide better services in drug innovation for customers. ■

Flying colours

The Centre for Drug Safety Evaluation and Research at SIMM, CAS provides a safety evaluation platform that meets international GLP standards. It obtained OECD's GLP certification in 2012, passed the GLP experimental project auditing by UK's Medicines and Healthcare Products Regulatory Agency (MHRA) in 2013 and the GLP evaluation on overall facility and experimental projects by US FDA in 2016.

On the home front, it won the national award for science and technology progress in 2013 and has completed safety evaluations for more than 200 new drug candidates, of which, 50 have been filed for clinical trial applications in China. Serving both domestic and international enterprises, it has assisted with obtaining more than 30 new drug certificates and clinical trial certificates, with no rejections. More than 80 of its safety evaluations are for clinical trial applications in the US or EU, with some having already won approval.

Capturing the moment

The First Affiliated Hospital of the Fourth Military Medical University has built an international-standard clinical evaluation platform, pushing China's GCP level higher. It has embraced global pharmacy ethics, being one of China's first hospitals to obtain the CAP certification of TCM clinical research ethics evaluation and having started application for the Association for the Accreditation of Human Research Protection Programs (AAHRPP) certification. It also has China's first ISO/IEC accredited testing and calibration laboratory and medical laboratory and boasts the first cardiovascular toxicity evaluation system in the Asia-Pacific region. The hospital has developed cutting-edge in-vivo biological sample analysis, including novel column chromatography techniques for chemical compound purification, and invented an electronic data capture system for new drug evaluation.

By mid-2015, the hospital had completed 269 new drug clinical evaluations, 21 of which are for class 1.1 new drugs. It is also the first in China to complete clinical evaluations for US National Cancer Institute projects.

Ding Lieming

The rise and rise of the Chinese pharmaceutical industry

By **Ding Lieming**, **Chairman & CEO, Betta Pharmaceuticals Co. Ltd.**

A prosperous and competitive pharmaceutical industry is typically supported by a healthy and sustainable innovation ecosystem. In China, fostered by supportive policies, a growing talent pool, and increased capital, the environment for biomedical innovation has greatly improved over the last ten years. The country's pharmaceutical companies are undergoing a shift from imitation to innovation.

The National Science and Technology Major Project for Drug Innovation launched in 2008, in particular, has driven remarkable achievements in drug innovation. These are demonstrated in many publications in high impact life science journals and the increasing international drug patent applications (968 obtained in 2015). Chinese companies have independently developed innovative drugs, such as icotinib, chidamide, apatinib and conbercept, highlighting their world-class research and development (R&D) capabilities in key domains. Typified by Hengrui, Betta, Chipscreen and many other success stories, a cluster of innovative pharmaceutical companies with international exposure and perspective has emerged.

Representative drug innovation products

Icotinib hydrochloride, hitting the domestic market in 2011 with the trade name, Conmana, is China's first independently developed small-molecule cancer drug. It is used in the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). It was credited with "kick-starting the Chinese anticancer drug industry" as "a milestone in oncology" when its phase III clinical study results were published on *The Lancet Oncology*. *Icotinib* was also listed in Pharma R&D Annual Review 2012 as one of 33 new drugs developed in 2011 worldwide, a first for a Chinese-invented drug.

On the home front, icotinib won the first prize of the National Science and Technology Progress Award in 2016, China's highest honour for science and technology achievements and the first time the chemical and pharmaceutical industry had won the prize. In the same year, icontinib also won the China Industry Award, that sector's top accolade. To date icotinib has total sales revenue of over 3 billion RMB and has benefited more than 100,000 patients.

Chidamide is a new molecular entity currently used for treating relapsed or refractory peripheral T-cell lymphoma (PTCL), a rare type of lymph-node cancer. It was independently developed by Chipscreen Biosciences and boasts a global patent protection. Approved for marketing by the China Food and Drug Administration (CFDA) in 2014 under the trade name, Epidaza, chidamide is also under clinical trials in the United States, Japan and Taiwan.

Chipscreen Biosciences, is another biotech enterprise founded by a group of Chinese with overseas experience in the United States. Specialized in R&D of small molecule drugs, the company

Joint ventures

Icotinib was developed after eight years of research by Betta Pharmaceuticals, a Chinese pharmaceutical company founded by entrepreneurs who earned their PhD degrees in the US. Devoted to developing new drugs with independent intellectual property rights, the company has set up a complete new drug R&D system and invested more than 13% of its annual revenue into R&D.

Betta Pharmaceuticals has more than ten other new drug projects in research, mostly targeting significant diseases such as cancer and diabetes. In 2013, it established a joint venture with the US-based Amgen to promote the marketing of a cancer drug, Vectibix, in China. In 2014, Betta worked with another American company, Xcovery, to develop a new-generation targeted drug for lung cancer, ensartinib, which is now under phase III clinical trial in the US and will soon be trialled in China.

currently has six new drug projects, which primarily target malignant tumour, diabetes and autoimmune diseases. Based on chemical genomics, Chipscreen has constructed an integrated technical system for drug innovation and early evaluation. With a technical and management team specialized in new drug R&D, it is capable of the whole-drug industrialization process, from target study to commercialization.

Apatinib mesylate (trade name: Aitan) is a new small-molecule target therapy drug for advanced gastric cancer, developed solely by Hengrui Medicine. Apatinib was approved for the Chinese market in October 2014 and is the world's first safe and effective target drug after the failure of standard chemotherapy. It is also the only orally-administered target drug against gastric cancer. Clinical studies are underway to test apatinib's effectiveness in treating liver, lung, breast and colorectal cancers.

Conbercept ophthalmic injection (trade name: Langmu) is a China-made, new-generation class-1 bio-drug for age-related macular degeneration. Developed by Chengdu Kanghong Pharmaceutical Group through ten years of research and at a cost of hundreds of millions RMB, the drug was approved to the market by CFDA in 2013 and has gained patent approval in China, United States, Russia, Korea and EU. Its clinical results were published in *Ophthalmology* and introduced in *Nature Reviews Drug Discovery*. Conbecept was included in WHO's International Nonproprietary Names List in 2012 and became China's first biological product with an internationally approved generic name.

Rapid progress of enterprises' drug R&D capabilities

There is still a gap in drug R&D capabilities between China and many Western countries. However, state policies encouraging innovation have attracted a critical mass of biomedical talent to return to China and boosted international collaboration in drug R&D. With these resources, many domestic pharmaceutical companies have gradually established their own drug R&D systems. Meanwhile, enterprises devoted to drug R&D are growing and generating great enthusiasm for innovation. More than 70 companies are active in the field, developing drugs targeting cancer, diabetes, and cardiovascular, infectious, autoimmune, and neuropsychiatric diseases.

In recent years, the growing popularity of antibody drugs has attracted many Chinese companies, who are conducting R&D of humanized antibodies, biosimilars, and antibody-drug conjugates (ADC). A typical representative is Alphamab Co. Ltd. in Suzhou. The company has established multiple highly efficient new platforms for antibody screening and engineering, which have successfully screened out several antibodies for clinical or preclinical studies, including KN035 targeting PD-L1 and several TNFR receptor agonists. Particularly, monoclonal antibody KN035, used for treating tumours, is China's first anti-PD-L1 drug and is approved by the US FDA to conduct clinical trials in the United States. More than 15 new drugs are currently under research at Alphamab.

Junshi Biosciences and BeiGene have also obtained CFDA approval for clinical trials for their PD-1 monoclonal antibody. CStone Pharma's recombinant anti-PD-L1 human monoclonal antibody was accepted by CFDA for review in October 2016.

Active participation in global cooperation

To drive innovation and internationalization, Chinese pharmaceutical companies are actively cooperating on a global level. Apart from clinical trials overseas, Chinese pharmaceuticals are also

collaborating with counterparts from abroad in product development and commercialization. In 2011, Hutchison Whampoa signed an agreement with AstraZeneca to promote the development, approval and sales of its volitinib worldwide. In 2013, BeiGene transferred to Merck the right to develop and sell its two products in overseas market. In 2015, Innovent Biologics and Eli Lilly reached an agreement on global development of three bispecific antibodies for cancer immunotherapy, with a milestone payment of over US$3.3 billion to Innovent, the largest amount for a biomedical project with Chinese and international cooperation. In the same year, Akeso Biopharma reached agreement with MSD for the latter to obtain exclusive global rights to develop and sell the Akeso-developed monoclonal antibody AK-107 for cancer immunotherapy, with up to US$200 million milestone payments.

Large Chinese pharmaceutical companies are also seeking to enrich their product portfolio by acquiring foreign companies. In November 2016, Luye Pharma Group, paid €245 million for the transdermal drug delivery system business from a Swiss company, Acino. In May 2016, the US unit of Humanwell Pharma Group acquired Epic Pharma and Epic RE Holdco for US$529 million and US$21 million respectively, and took over more than 30 products at various stages of development, covering therapeutic areas of narcotic analgesia, neurology and hypertension.

Several startup companies such as Ascletis Bioscience and Zai Lab are searching for early-stage products from foreign companies to develop them for global markets. Hua Medicine licensed worldwide rights to Roche's 4th generation glucokinase (GK) activator. Randomized, double-blind and placebo-controlled phase II clinical trial on type-2 diabetes in China showed significant reduction in blood glucose with good tolerance and safety, a first for good outcome for a 4th generation GK activator.

Significantly improved financing capabilities

In line with rapid growth, innovative pharmaceutical companies are becoming investment hotspots. Huge capital from outside the industry, including private equity funds and venture capital funds, are flowing in, providing a strong funding base for biomedical innovation.

In 2016, BeiGene and Hutchison Whampoa were listed on the US Nasdaq; Betta Pharmaceuticals was listed in the Shenzhen Stock Exchange. Meanwhile, Innovent Biologics received an investment of 1.7 billion RMB in Series C financing; Ascentage Pharma obtained 500 million RMB in Series B; and CStone Pharmaceuticals acquired more than US$100 million in its first round of financing.

Flourishing CRO companies

In light of the ever-rising cost of new drug R&D, many pharmaceutical companies are increasingly relying on low-cost contract research organizations (CROs) that provide comprehensive services, making CROs an important force supporting biomedical innovation.

Class leaders

For years, Hengrui Medicine has followed international standards to construct its drug R&D system. It has established five research centres and a clinical medicine department in China, the US and Japan and built a high-level R&D team of more than 1,200 staff. In addition to an R&D platform for small molecule drugs, it also has one for ADCs. In Hengrui's pipeline, 16 new drugs are under different phases of clinical trials.

China's CRO industry is flourishing, with the emergence of many pre-clinical CRO companies, represented by Wuxi AppTech, Medicilon, JOINN Laboratories and CrownBio, and CROs providing clinical research services, such as TigerMed and Fountain Medical Development. Composite growth rate of sales income for Chinese CRO industry reached 29.5% from 2007 to 2015.

CFDA's 2015 policy change requiring self-examination and consistency evaluation of clinical data sped up the selection process and enhanced the concentration of the CRO industry — leading CRO companies are presented with expansion opportunities, while the weak ones are weeded out.

In close collaboration with CROs, innovative drug R&D enterprises, especially the startups, developed new models that combine R&D and outsourcing for cooperative drug development. Their exploration propelled the development of innovative drugs in China.

Thanks to China's huge unmet clinical needs, continuous policy improvement, advancement of new drug R&D technologies, accumulation of fine talent and support from the capital market, Chinese pharmaceutical companies are well positioned to benefit patients at home and abroad with a greater range of high-quality drugs. ■