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Progress in Pharmacological Sciences in China

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Non-standard abbreviations:

NCEs, new chemical entities; CFDA, China Food and Drug Administration; NSFC, National Natural Science Foundation of China; SCI, science sitation index; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; AML, acute myeloid leukemia; PML, promyelocytic leukemia protein; CUEDC2, CUE (coupling of ubiquitin conjugation to ER degradation) domain-containing 2; IKK, IkB kinase; APC/C, anaphase-promoting complex or cyclosome; DFS, disease-free survival; JNK, c-Jun N-terminal kinase; RIP3, receptor-interacting protein 3; CaMKII, Ca^{2+}-calmodulin-dependent protein kinase; TRPV1, transient receptor potential vanilloid 1; 2-HG, 2-hydroxyglutarate; CAPON, carboxy-terminal PDZ ligand ; LHb, lateral habenula; CCR5, C-C motif chemokine receptor 5; GPCRs, G-protein-coupled receptors; CB1, Cannabinoid receptor 1; DMPK, drug metabolism and pharmacokinetics; OCT2, organic cation transporter 2; VRE, vancomycin-resistant enterococci; PCR, polymerase Chain reaction.

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Abstract

Pharmacology is the science that investigates the interactions between organisms and drugs and their mechanisms. Pharmacology plays a translational role in modern medicine, bridging basic research to the clinic. With its booming economy, China has invested an enormous amount of financial and human resources on pharmacological research in the recent decade. As a result, major breakthroughs have been achieved in both basic and clinical research in this area with the discoveries of many potential drug targets and biomarkers, making a sizable contribution to the overall advancement of pharmacological sciences. In this paper, we review recent research efforts and representative scientific achievements from China, and discuss future challenges and directions of pharmacological sciences in China.

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1. Introduction

During the past decade, many potential drug targets and biomarkers have been discovered as modern biomedical science enters a new area of rapid development with the emergence of new concepts and technologies. These achievements have been enabled by a multidisciplinary effort that derives from advancements in chemistry, pharmaceutics, pharmacology, medicine, and bioinformatics.

Pharmacology is a key field that studies the interplay between drugs and organisms and the underlying mechanisms, and plays important roles in the translation from basic research to clinical medicine. Discovery of innovative drugs and improvement of therapeutic efficacies of drugs are the most fundamental tasks for the development of pharmacology. R&D of new drugs in China has gained groundbreaking progress with the strong support of the Chinese government and enterprise investment. A number of representative new chemical entities (NCEs), including antofloxacin and icotinib, have been approved by the China Food and Drug Administration (CFDA). In addition, in 2016, Chinese investigators discovered more than 30 NCE candidates and applied for clinic trials in China (Data from the website of http://med.sina.com/article_detail_103/_2/_16713.html). These achievements would not have been possible without the progress of pharmacological sciences.

Pharmacology, as the cornerstone for the R&D of innovative drugs, is now faced with new opportunities and challenges. First, the development of life sciences and medical science has cultivated the revelation and clarification of mechanisms underlying disease occurrence and development. This not only promotes the discovery and validation of new drug targets, but also alters research ideas and methods in pharmacology. Secondly, pharmacological research has benefited greatly from the rapid progress of other modern sciences and technologies, such as imaging technology, high-throughput screening technology, theoretical and structural biology, computer technology, bioinformatics and other emerging technologies, which cumulatively give a huge boost to pharmacologists in conducting innovative investigations. Thirdly, the major battleground for new drug R&D currently focuses on major diseases, including tumors, metabolic diseases (e.g., diabetes),

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neurodegenerative diseases (e.g., Alzheimer's) and cardiovascular diseases (e.g., atherosclerosis). However, the pathogenic mechanisms and molecular regulation of these major diseases are very complex. The traditional pharmacological research model of "one drug, one disease" is being challenged, discarded, and replaced with new concepts to individualize treatment, taking into account different variables (e.g., ethnicity), in order to reduce the risks and cost of treatment. All of these new situations provide new directions and requirements for the development of pharmacological sciences.

The National Middle- and Long-term Scientific and Technological Development Plan (2006-2020) specifically designates the discovery and development of innovative drugs as one of the priority projects in the field of population and health in China. The National Natural Science Foundation of China (NSFC), the major funding agency in China, has been one of the most important sources of financial support for basic and clinical research of pharmacological sciences for many years. With the steady and continuous funding from government investments, China has been increasingly recognized as a major contributor to the global research in the area of pharmacological sciences with numerous high-quality research achievements. Here we summarize research efforts and representative achievements from China that have contributed to the development of pharmacological sciences.

2. Research funding and publications

In the past decade, the NSFC has initiated various Research Programs with a total funding of over 1.4 billion RMB in grants to support exploration in the pharmacological sciences. As shown in Fig. 1, funded grants and projects from NSFC experienced a healthy year-to-year increase between 2006 and 2015. In the last five years (2011 to 2015), the numbers of projects and funding dramatically increased to 2199 and 1.1 billion RMB, respectively, as compared to 1175 and 364 million RMB from 2006 to 2010. In particular, the NSFC supports and encourages pharmacological scientists to focus on the studies of novel mechanisms of drugs or bioactive products, the discovery and validation of new drug targets or biomarkers, structural and

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functional analysis of new drug targets, and personalization- and precision-based clinical pharmacology.

In addition to Research Programs, Talent Programs initiated by NSFC also play important roles in boosting the careers of outstanding young scientists. Many active Chinese researchers with study and/or work experience overseas have returned to China over the last 20 years preciously because of the generous support of governmental and institutional talent programs. These young scholars are now conducting creative research to become academic leaders in the forefront of clinical and basic research while making important contributions to the development of pharmacological sciences in China. Many important scientific achievements were contributed by these distinguished young scholars.

With the support of governmental funding, pharmacological research in China has been steadily leapfrogging. Chinese scientists in pharmacology are being increasingly recognized and acclaimed by the international community. The number of Science Citation Index (SCI)-cited publications in the field of Pharmacology and Pharmacy from China has gradually increased (Fig. 2). From 2006 to 2015, there were 350,855 publications in the world focused on Pharmacology and Pharmacy, to which China contributed 40,485 (11.54%). In particular, a significant increase was seen from 9.80% in 2010 to 17.48% in 2015 (Fig. 2). It is noteworthy that the proportion of highly-cited papers from China was significantly increased from 4.59% in 2010 to 11.22% in 2015 (Fig.2).

3. Representative achievements of pharmacological sciences in China

3.1 New mechanisms of drug action

Based on currently marketed drugs and candidate drugs in clinical trials, Chinese pharmacologists have investigated new mechanisms of efficacy, toxicity, and resistance in an attempt to identify new functions for the accurate classification of drugs and their use in personalized medicine, especially with respect to new mechanisms of anticancer-drugs.

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Notably, Chen and colleagues pioneered the use of arsenic to treat acute promyelocytic leukemia (APL). They demonstrated that combination therapy with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) achieved a significant remission (94.1%) in 85 APL patients, with a mild and reversible toxicity profile (Hu et al., 2009). This groundbreaking treatment regimen has now become the frontline therapy for *de novo* APL, which transforms APL into the first curable acute myeloid leukemia (AML). Moreover, this group has further revealed that the promyelocytic leukemia protein is a direct target of As_2O_3 (Zhang et al., 2010). Furthermore, another distinguished group of investigators led by Chen has revealed a new mechanism of drug action for adenanthin, a diterpenoid extracted from *Rabdosia adenantha*, which induces differentiation of APL cells by directly targeting peroxidase (Liu et al., 2012).

As the new era of personalized medicines emerges, research in China concerning oncological pharmacology has recently shifted its major focus to providing an integrative platform for the discovery and development of molecularly targeted anticancer therapies. Zhang and colleagues have demonstrated that the CUE (coupling of ubiquitin conjugation to ER degradation) domain-containing 2 (CUEDC2) protein can regulate many key cellular events, including cell cycle and inflammation (Li et al., 2008; Gao et al., 2011). Their follow-up study (Pan et al., 2011) has also uncovered that CUEDC2 can play a crucial role in the progression of breast cancer and act as therapeutic target by interacting with estrogen receptor-alpha (ER-α) protein. Collectively, these studies demonstrate the CUEDC2 serves as a new potential target for the treatments for inflammatory diseases and tumors.

3.2 New drug targets

Discovery of new drug targets is the bedrock to find novel drugs in a fast, efficient, and sustainable research mode. Recently, many Chinese pharmacologists have made great strides in the discovery and functional verification of new drug targets.

The YAP/TAZ signaling pathway was initially reported as a key regulator of cell size during embryogenesis, although later investigations revealed a pro-carcinogenic

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role for this axis. Huang and colleagues provided novel evidence to show that endothelial YAP/TAZ activation induced by atheroprone-disturbed flow promotes inflammation and atherogenesis by enhancing the activity of c-Jun N-terminal kinase (JNK) (Wang et al., 2016). Coincidently, several anti-atherosclerotic drugs and especially statins can effectively inhibit the YAP/TAZ pathway, indicating that YAP/TAZ may become a potential therapeutic target against atherosclerosis.

Recently, Xiao and co-workers revealed a previously unappreciated regulatory role for receptor-interacting protein 3 (RIP3) in necroptosis, and provided a potential therapeutic target in myocardial infarction. They discovered that the novel RIP3-CaMKII-mPTP pathway provides a potential target for the treatment of ischemia-induced and oxidative stress-induced myocardial damage (Zhang et al., 2016). With respect to hypertension, Zhu and colleagues reported that the activated transient receptor potential vanilloid 1 (TRPV1) can induce the production of nitric oxide (NO) in endothelial cells, which may indicate a potential target for the treatment of hypertension (Yang et al., 2010).

Similar work in anti-cancer drug discovery has also come to fruition. Lin and colleagues revealed that activating the GSK3-TIP60-ULK1 signaling pathway can integrate protein phosphorylation and acetylation in the regulation of autophagy induced by growth factor deprivation, thus providing a new target for anti-tumor drugs that regulates tumor cell autophagy (Lin et al., 2012). Zhao and Colleagues demonstrated that the intracellular accumulation of 2-hydroxyglutarate (2-HG), an inhibitor of α-KG-dependent dioxygenases, can alter cell proliferation and growth by inhibiting the activity of dioxygenases (Xu et al., 2011). Lei and co-workers revealed that lysine-5 acetylation decreases LDH-A activity and consequently significantly inhibits cell proliferation and tumor migration, arguing that LDH-A acetylation could be targeted for the early diagnosis and treatment of pancreatic cancer (Zhao et al., 2013).

Trailblazing research in China has also brought hope to millions of patients with neuropsychiatric disorders such as anxiety and depression. Zhu and co-workers have recently shown that the binding between nNOS and CAPON can result in the

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modulation of anxiety-related behaviors by regulating Dexras1-ERK signaling. They have also demonstrated that significant anxiolytic-like effects are rapidly produced by small-molecule blockers of nNOS-CAPON binding (Zhu et al., 2014). However, the pathogenesis and molecular mechanisms of depression still remain unknown. It is noteworthy that Hu and colleagues provided convincing evidence emphasizing the roles of β-calcium/calmodulin-dependent protein kinase type II (βCaMKII) in depression (Li et al., 2013), thus verifying lateral habenula (LHb) as a new target for treatment. We believe that a deeper understanding of the mechanisms underlying anxiety is benefit for the development of new anxiolytic agents.

3.3 Structural pharmacology

With its combination of structural biology and pharmacology, the emergence of structural pharmacology, as a new field of pharmacological sciences, is playing an unprecedented role in the R&D of new drugs in China. Through high-resolution analysis of CCR5 conformation, Wu and colleagues demonstrated that HIV-1 co-receptor selectivity mainly depends on steric hindrance and charge distribution associated with residue substitutions. This result will enable structure-based drug discovery for the treatment of HIV-1 infection (Tan et al., 2013).

P2Y12 receptor (P2Y12R), a purinergic G-protein-coupled receptor (GPCR), plays crucial roles in platelet activation and thrombus formation. Recently, Zhao and co-workers provided detailed maps of P2Y12R crystal structure, including the 2.5Å resolution structure of P2Y12R binding to the agonist 2MeSADP, the 3.1Å resolution structure of P2Y12R bound to the partial agonist 2MeSATP, and the 2.6Å resolution structure of P2Y12R bound to the antagonist AZD1283. Through comparison of the structures of the three different complexes, the mechanisms involved in accelerating or slowing thrombus formation, based on the interaction between receptor and drug molecules, have been clearly elucidated (Zhang et al., 2014a; Zhang et al., 2014b).

In 2013, Xu and colleagues reported a high-resolution crystal structure of human ten-eleven-translocation 2 (TET2) bound to methylated DNA. This high-resolution analysis of TET2 conformation will facilitate our understanding of the mechanisms of

TET-mediated 5mC oxidation and subsequent structure-based drug discovery for myeloid leukemia (Hu et al., 2013).

Recently, cannabinoid receptor 1 (CB1) has been identified as a promising therapeutic target for many diseases, including inflammation, pain, and substance abuse disorders. In order to understand the mechanisms underlying the physiological functions of CB1, and to design the next-generation of CB1-targeting drugs, a high resolution analysis of human CB1 binding to antagonist AM6538 was reported by Liu and colleagues. These investigators showed that the CB1-AM6538 complex plays a critical role in antagonist binding (Hua et al., 2016). These lines of research will continue to unravel new modes of actions for potential drug targets.

3.4 Clinical pharmacology

Clinical pharmacology bridges the translation from basic research to clinical medicine. Research in clinical pharmacology is mainly focused on pharmacokinetics, pharmacodynamics, drug-drug interactions, drug resistance, pharmacogenetics, pharmacogenomics, and clinical trials of new drugs. In recent years, clinical pharmacologists in China have made great progress in clinical drug evaluationwith the aim of providing guidance for advances in rational and personalized medicine.

Zhou and colleagues are pioneers in pharmacogenetics and pharmacogenomics in China (Zhou et al., 1989). They have reported gene polymorphisms in a number of important drug metabolizing enzymes, drug transporters, and receptors among various Chinese ethnic groups. In the last decade, they have constructed comprehensive mathematical models and algorithms that incorporate both clinical and genetic factors to predict clinical dosages of warfarin, tacrolimus, and *cis*-platin on the basis of large sample clinical trials. These have been included in the personalized medicine guidelines published by the National Health and Family Planning Commission of China (Luo et al., 2017). Besides Zhou and colleagues, other distinguished groups are also active in clinical pharmacology research in China. Zeng and colleagues were the first to develop recombinant drug metabolizing enzymes and cell models with stably over-expressed drug transporters for studies of drug metabolism and

pharmacokinetics (DMPK) in China. The tools that they have provided include more than 50 human recombinant enzymes, such as CYPs, UGTs, GSHs, ADH, and AKR, as well as ~30 cell lines with stably over-expressed drug transporters, such as MDR1, BCRP, OCTs, OATs, and MRPs. Recently, research in this group has focused on the epigenetic mechanisms responsible for the silencing of drug transporters in cancer cells. They have reported that aberrant DNA methylation surrounding the human organic cation transporter 2 (OCT2) promoter could be responsible for OCT2 repression in renal cell carcinoma (RCC), thus providing proof-of-concept for novel targeted therapies (Liu et al., 2016). Zhong and colleagues have used a genome-wide association study to identify new genetic loci that modify antiplatelet effects in Chinese patients with coronary heart disease (Zhong et al., 2016). In a randomized, double-blind clinical trial with 20,702 adult hypertensive patients, Huo and colleagues revealed that the combined use of enalapril and folic acid could significantly reduce the risk of first stroke, when compared to enalapril alone (Huo et al., 2015).

Antibiotic resistance is one of the major issues that requires the constant attention of clinical pharmacologists. Glycopeptides, including vancomycin and teicoplainin, have broad activities against gram-positive bacteria and are usually considered for the treatment of life-threatening infections induced by gram-positive pathogens. VanA and vanB are usually considered to be the two most predominant genotypes of vancomycin-resistant enterococci (VRE) worldwide. In 2010, a new glycopeptide resistance genotype, VanM, was found by Wang and colleagues in a clinical strain of *Enterococcus faecium* Efm-HS0661 in Shanghai. Similar to the VanA type, VanM confers high-level resistance to glycopeptides (Xu et al., 2010). Recently, a new statistical analysis was reported by the same research group showing that VanM (64.3%, 45/70) was more prevalent than VanA (35.7%, 25/70) in 70 VRE strains collected from 9 hospitals in Shanghai during 2006-2014 (Chen et al., 2015).

4. Perspectives

Following the release of China's 13th Five-Year Innovation Plan of National Science and Technology, great opportunities have been bestowed upon the Chinese

pharmaceutical industry. However, we are acutely aware of the fact that there are many challenges and unsolved problems in the progress of pharmacological sciences. First, highly cited papers on pharmacology from China are generally below the average level of world, the percentage of highly cited papers from China only accounted for 5.32% of world publications in the same field (Fig.2). Secondly, the development of different branches of pharmacological sciences is still imbalanced, with more than 50% of research papers and research funding distributed to antineoplastic pharmacology, cardio-cerebral vascular pharmacology, and neuropsychiatric pharmacology, while personalized medicine, drug target discovery and validation, stem cell pharmacology, and structural pharmacology are under-funded. Moreover, we need to encourage highly talented and experienced research leaders to enthusiastically engage in promoting international collaboration between China and other countries.

Future directions in pharmacological sciences in China will continue to focus on the discovery and validation of innovative drugs, using modern technologies to identify active components in traditional Chinese herbs and promoting new uses of old drugs. With this in mind, the NSFC will continue to support research directed toward the discovery and verification of new drug targets and biomarkers, structural pharmacology, epigenetics-based pharmacology, stem cell-based regenerative pharmacology, molecular pharmacology, and clinical pharmacology. With continued support both in funding and in policy, we believe that a steady and greater progress in pharmacological science will be achieved in China.

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Figure legends

Figure 1 Total numbers of grants and total funding for pharmacological sciences projects supported by NSFC from 2006 to 2015. The data were provided by NSFC.

Figure 2 The number of publications from China and the world in pharmacology and pharmacy from 2006 to 2015. The number of publications (articles and reviews) and highly-cited papers are based on Web of Science Database Science Citation Index Expanded in the field of Pharmacology and Pharmacy up to December 18, 2016; these data were provided by Clarivate Analytics and analyzed with InCites.

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Figure 1

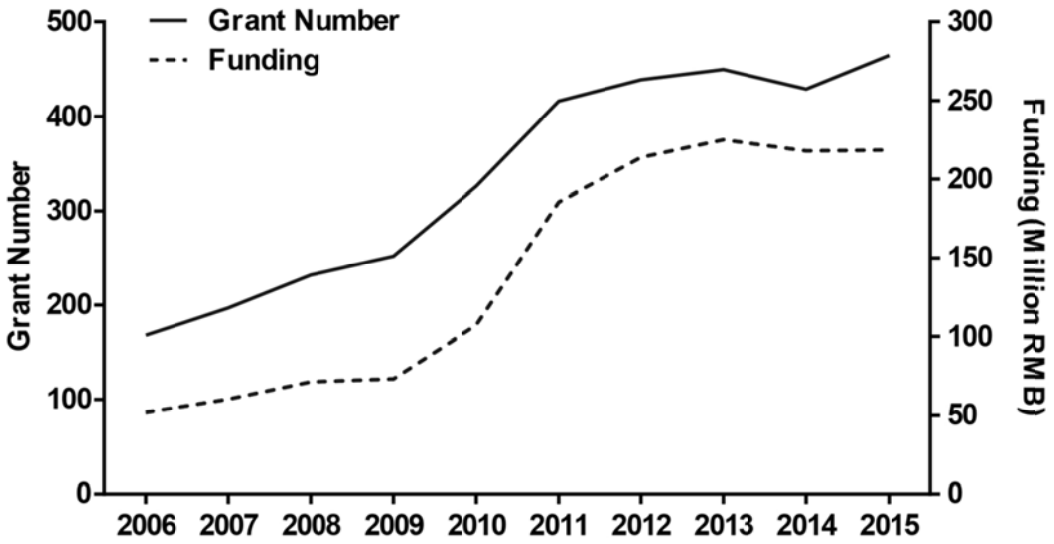

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Figure 2