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MINIREVIEW—MOLECULAR PHARMACOLOGY IN CHINA

Progress in Pharmacological Sciences in China

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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 and the clinic. With its economy booming, China has invested an enormous amount of financial and human resources in pharmacological research in the recent decade. As a result, major breakthroughs have been achieved in both basic and clinical research, with the discovery of many potential drug targets and biomarkers that has made a sizable contribution to the overall advancement of pharmacological sciences. In this article, we review recent research efforts and representative scientific achievements and discuss future challenges and directions for the pharmacological sciences in China.

Introduction

During the past decade, many potential drug targets and biomarkers have been discovered, as modern biomedical science entered a new area of rapid development along with the emergence of new concepts and technologies. These achievements have been enabled by multidisciplinary efforts derived 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 of basic research to clinical medicine. The discovery of innovative drugs and improvement of therapeutic efficacy are the most fundamental tasks in the development of pharmacology. R&D of new drugs in China has made 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. In addition, in 2016, Chinese investigators discovered more than 30 NCE candidates and applied for clinic trials in China (data from the website [in Chinese] http://med.sina.com/article_detail_103/_2/_16713.html). These achievements would not have been possible without the progress that occurred in the 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 and medical sciences is focused on revealing and clarifying 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. Second, pharmacological research benefits 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 conducting innovative investigations. Third, the major battleground for new drug R&D is currently the major diseases, including tumors, metabolic diseases (e.g., diabetes), neurodegenerative diseases (e.g., Alzheimer's), and cardiovascular diseases (e.g., atherosclerosis). However, the pathogenic mechanisms and molecular regulation of major diseases are very complex. The traditional pharmacological research model of "one drug, one disease" is being challenged, discarded, and replaced with new concepts of individualized treatment that take 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.

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ABBREVIATIONS: 5mC, 1,2-dihydro-1,2-dihydroxy-5-methylchrysene; AM6538, 4-{4-[1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-yl)-carbamoyl]-1H-pyrazol-5-yl]phenyl}but-3-yn-1-yl nitrate; APL, acute promyelocytic leukemia; AZD1283, 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester; CB1, cannabinoid receptor 1; CUEDC2, CUE (coupling of ubiquitin conjugation to ER degradation) domain-containing 2; KG, 2-oxopentanedioic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NCE, new chemical entity; NSFC, National Natural Science Foundation of China; OCT, organic cation transporter; RMB, renminbi; TET, ten-eleven-translocation.

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 in pharmacological sciences for many years. With steady and continuous funding from government investment, China is increasingly recognized as a major contributor to global research in pharmacological sciences because of its numerous high-quality research achievements. Here we summarize research efforts and representative achievements from China that have contributed to the development of pharmacological sciences.

Research Funding and Publications

In the past decade, the NSFC has initiated various Research Programs with a total funding of over 1.4 billion renminbi (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 5 years (2011–2015), the number of projects and funding dramatically increased to 2199 and 1.1 billion RMB, respectively, compared with 1175 and 364 million RMB from 2006 to 2010. In particular, the NSFC supports and encourages studies of novel mechanisms of drugs or bioactive products, the discovery and validation of new drug targets or biomarkers, structural and 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 an important role 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 precisely because of the generous support of governmental and institutional talent programs. These young scholars are now conducting creative research that will place them at the forefront of clinical and basic research, at the same time as they make important contributions to the development of pharmacological sciences in China. Many important scientific achievements have already been credited to them.

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–cited publications from China in the fields of pharmacology and pharmacy 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 has increased significantly—from 4.59% in 2010 to 11.22% in 2015 (Fig. 2).

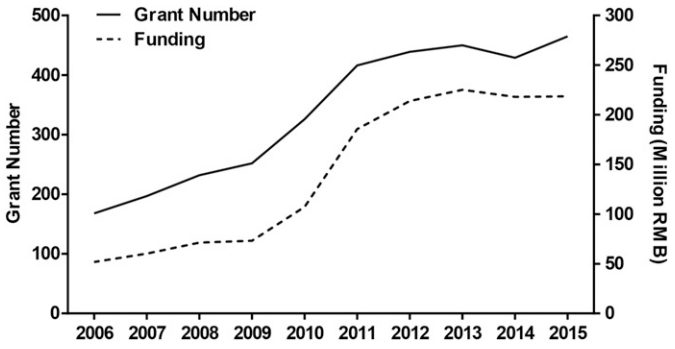

Fig. 1. Total numbers of grants and total funding for pharmacological sciences projects supported by NSFC from 2006 to 2015 (data provided by NSFC).

Representative Achievements of Pharmacological Sciences in China

New Mechanisms of Drug Action. With several currently marketed drugs and candidate drugs in clinical trials as a result, Chinese pharmacologists have been investigating new mechanisms of efficacy, toxicity, and resistance in an attempt to identify new functions that enable more accurate classification of drugs and their use in personalized medicine. This is especially true with respect to anticancer drugs.

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 and arsenic trioxide achieved a significant remission rate (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. Moreover, this group has further revealed that the promyelocytic leukemia protein is a direct target of arsenic trioxide (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* that 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 primary focus to providing an integrative platform

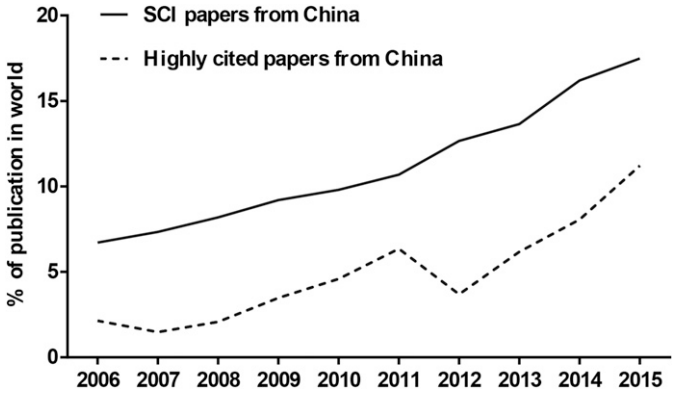

Fig. 2. The number of publications from China and the world in pharmacology and pharmacy from 2006 to 2015. The number of publications (articles and reviews) and highly-cited papers was compiled on the basis of the Web of Science Databases, Science Citation Index Expanded in the fields of pharmacology and pharmacy up to December 18, 2016 (data provided by Clarivate Analytics and analyzed with InCites).

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) also uncovered a crucial role that CUEDC2 can play in the progression of breast cancer, and its potential as a therapeutic target through its interaction with estrogen receptor-alpha (ER-α) protein. Collectively, these studies demonstrate that CUEDC2 serves as a new potential target for the treatments for inflammatory diseases and tumors.

New Drug Targets. Discovery of new drug targets is the foundation for finding 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 procarcinogenic 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 (Wang et al., 2016). Coincidently, several antiatherosclerotic 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 coworkers revealed a previously unappreciated regulatory role in necroptosis for receptor-interacting protein 3 (RIP3) and thus provided a potential therapeutic target in myocardial infarction. They discovered that the novel RIP3-Ca^{2+}-calmodulin–dependent protein kinase (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 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 anticancer drug discovery has also come to fruition. Lin and colleagues (2012) 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 antitumor drugs to regulate tumor cell autophagy. 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 coworkers 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 coworkers (2014) have recently shown that the binding between nNOS and carboxy-terminal PDZ ligand (CAPON) can result in the 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. 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 the lateral habenula as a new target for treatment. We believe that a deeper understanding of the mechanisms underlying anxiety will be of benefit to the development of new anxiolytic agents.

Structural Pharmacology. With its combination of structural biology and pharmacology, structural pharmacology is emerging as a new field of pharmacological sciences and is playing an unprecedented role in the R&D of new drugs in China. Through high-resolution analysis of C-C motif chemokine receptor 5 conformation, Wu and colleagues demonstrated that HIV-1 coreceptor 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, plays crucial roles in platelet activation and thrombus formation. Recently, Zhao and coworkers provided detailed maps of P2Y12R crystal structure, including the 2.5-Å resolution structure of P2Y12R binding to the agonist 2MeSADP, the 3.1-Å resolution structure of P2Y12R bound to the partial agonist 2-methylthio-ATP (2MeSATP), and the 2.6-Å 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 have been clearly elucidated on the basis of the interaction between receptor and drug molecules (Zhang et al., 2014a,b).

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. To understand the mechanisms underlying the physiologic 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.

Clinical Pharmacology. Clinical pharmacology bridges the translation of 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 evaluation, with the aim of providing guidance for advances in rational and personalized medicine.

Zhou and colleagues (1989) are pioneers in pharmacogenetics and pharmacogenomics in China. 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 cisplatin, 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 overexpressed drug transporters for studies of drug metabolism and pharmacokinetics in China. The tools that they have provided include more than 50 human recombinant enzymes, such as cytochrome P450s, UGTs, GSHs, ADH, and AKR, as well as ~30 cell lines with stably overexpressed drug transporters, such as MDR1, BCRP, organic cation transporters (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 OCT2 promoter could be responsible for OCT2 repression in renal cell carcinoma, thus providing proof-of-concept for novel targeted therapies (Liu et al., 2016). Zhong and colleagues (2016) have used a genome-wide association study to identify new genetic loci that modify antiplatelet effects in Chinese patients with coronary heart disease. In a randomized, double-blind clinical trial with 20,702 adult hypertensive patients, Huo and colleagues (2015) revealed that the combined use of enalapril and folic acid could significantly reduce the risk of first stroke, when compared with enalapril alone.

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 the two predominant genotypes of vancomycin-resistant enterococci worldwide. In 2010, a new glycopeptide-resistant genotype, VanM, was found by Wang and colleagues in a clinical strain of *Enterococcus faecium* Efm-HS0661 in Shanghai. Like 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 vancomycin-resistant enterococci strains collected from nine hospitals in Shanghai during 2006–2014 (Chen et al., 2015).

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 that there are many challenges and unsolved problems in the progress of pharmacological sciences. First, the citation of papers on pharmacology from China is generally below the average level of the world; the percentage of highly cited papers from China only accounted for 5.32% of world publications in the same field (Fig. 2). Second, the development of different branches of pharmacological sciences is still unbalanced, with more than 50% of research papers and research funding distributed to antineoplastic pharmacology, cardiocerebral vascular pharmacology, and neuropsychiatric pharmacology, whereas personalized medicine, drug target discovery and validation, stem cell pharmacology, and structural pharmacology are underfunded. 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 steady and even greater progress in pharmacological science will be achieved in China.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Wang, Zhu, Wu, Dong.

References

Chen C, Sun J, Guo Y, Lin D, Guo Q, Hu F, Zhu D, Xu X, and Wang M (2015) High Prevalence of vanM in Vancomycin-Resistant Enterococcus faecium Isolates from Shanghai, China. *Antimicrob Agents Chemother* **59**:7795–7798.

Gao YF, Li T, Chang Y, Wang YB, Zhang WN, Li WH, He K, Mu R, Zhen C, Man JH, et al. (2011) Cdk1-phosphorylated CUEDC2 promotes spindle checkpoint inactivation and chromosomal instability. *Nat Cell Biol* **13**:924–933.

Hu L, Li Z, Cheng J, Rao Q, Gong W, Liu M, Shi YG, Zhu J, Wang P, and Xu Y (2013) Crystal structure of TET2-DNA complex: insight into TET-mediated 5mC oxidation. *Cell* **155**:1545–1555.

Hu J, Liu YF, Wu CF, Xu F, Shen ZX, Zhu YM, Li JM, Tang W, Zhao WL, Wu W, et al. (2009) Long-term efficacy and safety of all-trans retinoic acid/arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci USA* **106**:3342–3347.

Hua T, Vemuri K, Pu M, Qu L, Han GW, Wu Y, Zhao S, Shui W, Li S, Korde A, et al. (2016) Crystal Structure of the Human Cannabinoid Receptor CB1. *Cell* **167**: 750–762.e14.

Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, Tang G, Wang B, Chen D, He M, et al.; CSPPT Investigators (2015) Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA* **313**:1325–1335.

Li HY, Liu H, Wang CH, Zhang JY, Man JH, Gao YF, Zhang PJ, Li WH, Zhao J, Pan X, et al. (2008) Deactivation of the kinase IKK by CUEDC2 through recruitment of the phosphatase PP1. *Nat Immunol* **9**:533–541.

Li K, Zhou T, Liao L, Yang Z, Wong C, Henn F, Malinow R, Yates, 3rdJR, and Hu H (2013) βCaMKII in lateral habenula mediates core symptoms of depression. *Science* **341**:1016–1020.

Lin SY, Li TY, Liu Q, Zhang C, Li X, Chen Y, Zhang SM, Lian G, Liu Q, Ruan K, et al. (2012) GSK3-TIP60-ULK1 signaling pathway links growth factor deprivation to autophagy. *Science* **336**:477–481.

Liu CX, Yin QQ, Zhou HC, Wu YL, Pu JX, Xia L, Liu W, Huang X, Jiang T, Wu MX, et al. (2012) Adenanthin targets peroxiredoxin I and II to induce differentiation of leukemic cells. *Nat Chem Biol* **8**:486–493.

Liu Y, Zheng X, Yu Q, Wang H, Tan F, Zhu Q, Yuan L, Jiang H, Yu L, and Zeng S (2016) Epigenetic activation of the drug transporter OCT2 sensitizes renal cell carcinoma to oxaliplatin. *Sci Transl Med* **8**:348–397.

Luo Z, Li X, Zhu M, Tang J, Li Z, Zhou X, Song G, Liu Z, Zhou H, and Zhang W (2017) Identification of novel variants associated with warfarin stable dosage by use of a two-stage extreme phenotype strategy. *J Thromb Haemost* **15**:28–37.

Pan X, Zhou T, Tai YH, Wang C, Zhao J, Cao Y, Chen Y, Zhang PJ, Yu M, Zhen C, et al. (2011) Elevated expression of CUEDC2 protein confers endocrine resistance in breast cancer. *Nat Med* **17**:708–714.

Tan Q, Zhu Y, Li J, Chen Z, Han GW, Kufareva I, Li T, Ma L, Fenalti G, Li J, et al. (2013) Structure of the CCR5 chemokine receptor-HIV entry inhibitor maraviroc complex. *Science* **341**:1387–1390.

Wang L, Luo JY, Li B, Tian XY, Chen LJ, Huang Y, Liu J, Deng D, Lau CW, Wan S, et al. (2016) Integrin-YAP/TAZ-JNK cascade mediates atheroprotective effect of unidirectional shear flow. *Nature* **540**:579–582.

Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Wang P, Xiao MT, et al. (2011) Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell* **19**:17–30.

Xu X, Lin D, Yan G, Ye X, Wu S, Guo Y, Zhu D, Hu F, Zhang Y, Wang F, et al. (2010) vanM, a new glycopeptide resistance gene cluster found in Enterococcus faecium. *Antimicrob Agents Chemother* **54**:4643–4647.

Yang D, Luo Z, Ma S, Wong WT, Ma L, Zhong J, He H, Zhao Z, Cao T, Yan Z, et al. (2010) Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. *Cell Metab* **12**: 130–141.

Zhang J, Zhang K, Gao ZG, Paoletta S, Zhang D, Han GW, Li T, Ma L, Zhang W, Müller CE, et al. (2014a) Agonist-bound structure of the human P2Y12 receptor. *Nature* **509**:119–122.

Zhang K, Zhang J, Gao ZG, Zhang D, Zhu L, Han GW, Moss SM, Paoletta S, Kiselev E, Lu W, et al. (2014b) Structure of the human P2Y12 receptor in complex with an antithrombotic drug. *Nature* **509**:115–118.

Zhang T, Zhang Y, Cui M, Jin L, Wang Y, Lv F, Liu Y, Zheng W, Shang H, Zhang J, et al. (2016) CaMKII is a RIP3 substrate mediating ischemia- and oxidative stress-induced myocardial necroptosis. *Nat Med* **22**:175–182.

Zhang XW, Yan XJ, Zhou ZR, Yang FF, Wu ZY, Sun HB, Liang WX, Song AX, Lallemand-Breitenbach V, Jeanne M, et al. (2010) Arsenic trioxide controls the fate of the PML-RARalpha oncoprotein by directly binding PML. *Science* **328**:240–243.

Zhao D, Zou SW, Liu Y, Zhou X, Mo Y, Wang P, Xu YH, Dong B, Xiong Y, Lei QY, et al. (2013) Lysine-5 acetylation negatively regulates lactate dehydrogenase A and is decreased in pancreatic cancer. *Cancer Cell* **23** DOI: 10.1016/j.ccr.2013.02.005.

Zhong WP, Wu H, Chen JY, Li XX, Lin HM, Zhang B, Zhang ZW, Ma DL, Sun S, Li HP, et al. (2016) Genomewide association study identifies novel genetic loci that modify antiplatelet effects and pharmacokinetics of clopidogrel. *Clin Pharmacol Ther* DOI:10.1002/cpt.589.

Zhou HH, Koshakji RP, Silberstein DJ, Wilkinson GR, and Wood AJ (1989) Racial differences in drug response. Altered sensitivity to and clearance of propranolol in men of Chinese descent as compared with American whites. *N Engl J Med* **320**:565–570.

Zhu LJ, Li TY, Luo CX, Jiang N, Chang L, Lin YH, Zhou HH, Chen C, Zhang Y, Lu W, et al. (2014) CAPON-nNOS coupling can serve as a target for developing new anxiolytics. *Nat Med* **20**:1050–1054.

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