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Review Article

Paving the way for small-molecule drug discovery

Yu-Shui Ma[1,2,3*], Rui Xin[3*], Xiao-Li Yang[3*], Yi Shi[2*], Dan-Dan Zhang[3*], Hui-Min Wang[2], Pei-Yao Wang[3], Ji-Bin Liu[2], Kai-Jian Chu[4], Da Fu[3]

[1]National Engineering Laboratory for Deep Process of Rice and Byproducts, College of Food Science and Engineering, Central South University of Forestry and Technology, Changsha 410004, Hunan, China; [2]Cancer Institute, Nantong Tumor Hospital, Nantong 226631, China; [3]Central Laboratory for Medical Research, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China; [4]Department of Biliary Tract Surgery I, Third Affiliated Hospital of Second Military Medical University, Shanghai 200438, China. [*]Equal contributors.

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Abstract: Small-molecule drugs are organic compounds affecting molecular pathways by targeting important proteins, which have a low molecular weight, making them penetrate cells easily. Small-molecule drugs can be developed from leads derived from rational drug design or isolated from natural resources. As commonly used medications, small-molecule drugs can be taken orally, which enter cells to act on intracellular targets. These characteristics make small-molecule drugs promising candidates for drug development, and they are increasingly favored in the pharmaceutical market. Despite the advancements in molecular genetics and effective new processes in drug development, the drugs currently used in clinical practice are inadequate due to their poor efficacy or severe side effects. Therefore, developing new safe and efficient drugs is a top priority for disease control and curing.

Keywords: Small-molecule drugs, compound, natural resource, molecular genetics, cancer

Small-molecule drugs are organic compounds affecting molecular pathways by targeting important proteins, which have a low molecular weight, making them penetrate cells easily. Small-molecule drugs can be developed from leads derived from rational drug design or isolated from natural resources [1-3]. As commonly used medications, small-molecule drugs can be taken orally, which enter cells to act on intracellular targets [4]. These characteristics make small-molecule drugs promising candidates for drug development, and they are increasingly favored in the pharmaceutical market [5-7]. Despite the advancements in molecular genetics and effective new processes in drug development, the drugs currently used in clinical practice are inadequate due to their poor efficacy or severe side effects. Therefore, developing new safe and efficient drugs is a top priority for disease control and curing. Since the beginning of the 21st century, all basic scientific disciplines have developed rapidly, and the resulting knowledge and techniques have been applied to the medical field [8-11].

This review summarizes the basic approaches of research to discover small-molecule drugs. Research strategies for discovering breakthrough drugs consist of discovery of lead compounds and optimization of lead compounds, each of which play important roles in how these drugs ultimately reach the pharmaceutical market (**Figure 1**) [12-15].

Discovery of lead compounds

Lead compounds can be obtained from natural sources (e.g., animals, plants, and microorganisms), and their physiological processes as well as drug metabolites produced from exogenous drug applications. Prospective lead compounds can be further screened and optimized via observations of clinical side effects of tested drugs [16-19].

Obtaining lead compounds from natural products

The search for natural products and the comprehensive analysis of their novel structural, chemical, and pharmacological characteristics represent an important pathway for lead compound discovery [20]. According to statistics, approximately half of the clinical drugs currently on the market are derived from natural products and their derivatives [21-23]. For example,

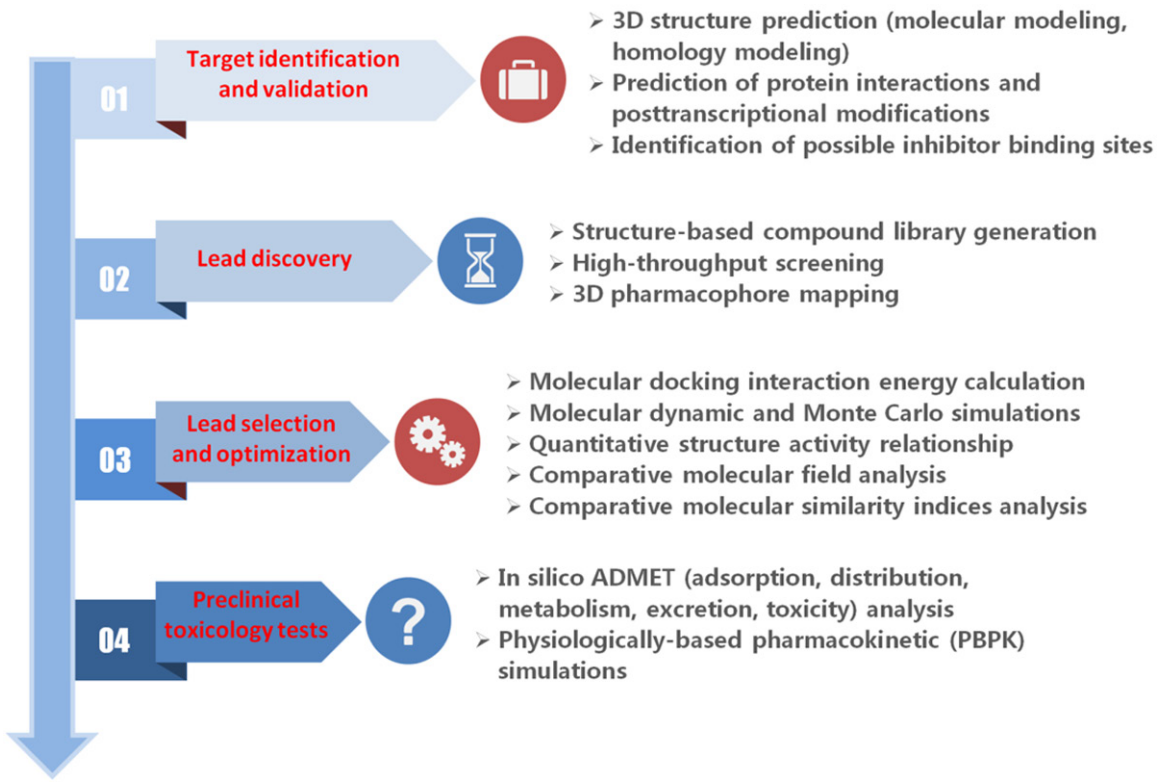

Figure 1. Workflow of *in silico* approaches for small molecule drug discovery. The path leading to the development of a new drug is long and complex, representing the convergence of *in silico* and *in vitro* screenings and *in vitro* and *in vivo* testing and validation, which highlight the need for a faster track in the procedures for drug development to be met by increasing the *in silico* part of the process, performing via digital computing a series of time-saving evaluations that can greatly simplify the *in vitro* procedures.

morphine was isolated from opium in 1808. In the 1960s, the antibiotic cephalosporin C was obtained from metabolites of cephalosporins, and a series of semi-synthetic antibiotics with considerable antibacterial activities and wide antibacterial spectra were obtained by modifying the side chains of seven amino groups [24].

In 1972, Chinese scientists isolated artemisinin from Artemisia annua L, and, through structural modification, developed artemether, artesunate, and dihydroartemisin, all of which have been shown to exhibit more effective antimalarial activities than the originally isolated artemisinin [25-27]. In recent years, the United States isolated the anticancer active ingredient, paclitaxel, from the taxol plant, which has been approved for commercial use and is the drug of choice for clinical treatment of ovarian cancer [28].

Obtaining a lead compound from an intermediate

During the synthesis of a drug, many intermediates appear, and the structures of these intermediates and final products are often similar to one another and to the original drug [29]. Screening these compounds to obtain pharmacologically active structures is one way to obtain lead compounds (**Figure 2**) [30-32]. For example, from the synthesis of the antitumor drug, cytarabine, the intermediate, cyclocytidine, is obtained and also exhibits antitumor activity [33]. Compared with cytarabine, cyclocytidine has additional advantages in terms of its slow metabolism in the body, long duration of action, and minimal effects, all of which have led it to become a clinical drug for leukemia treatment [34-37].

Obtaining lead compounds from basic research

The rapid development of biochemistry, molecular biology, pharmacology, and other related disciplines has provided the basis and means for the improved research and development of small-molecule drugs. This period of development also provided novel targets and lead compounds for the design of small-molecule drugs,

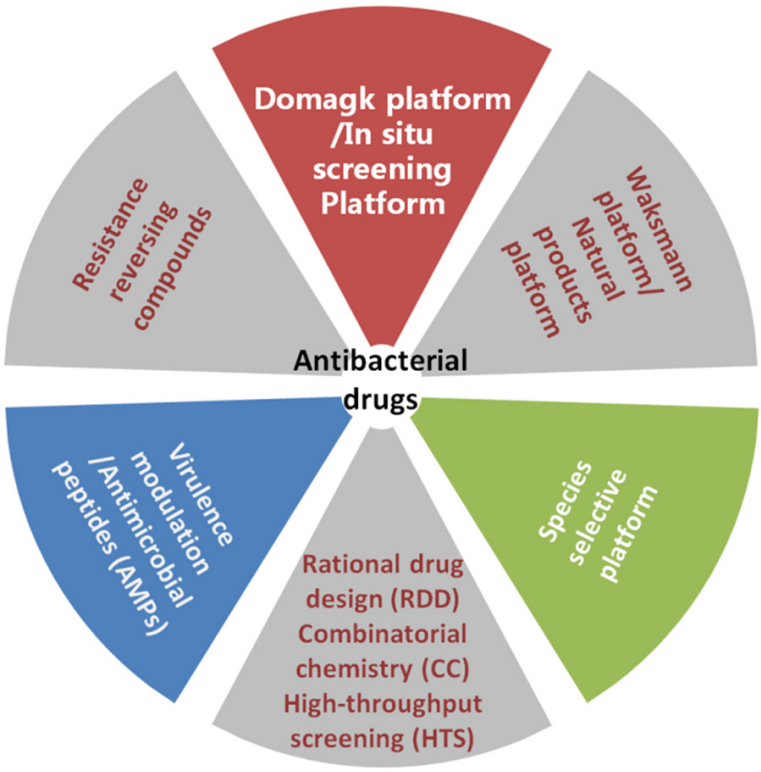

Figure 2. Overview of various discovery platforms for antibacterial drugs. There is a very low probability for a biologically active compounds to succeed from the pre-clinical to clinical phase of drug discovery. For this reason, reliable discovery platforms are needed to continuously produce compounds with antibacterial activity that may be lead compounds for further studies. The currently defined antibiotic discovery platforms are summarized.

such as enzymes, receptors, ion channels, and nucleic acids [38-41]. On this basis, researchers have conducted in-depth studies on the mechanisms of action of enzymes and receptors in the body [42].

According to the structures and performances of drug targets, molecular engineering methods have been used to design various molecules (**Figure 3**) [43-45]. Enzymatic inhibitors, receptor agonists/antagonists, and channel blockers have all been successfully designed [46-49]. For example, the renin-angiotensin-aldosterone system is active in hypertensive patients, in which angiotensin-converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II, while angiotensin II can contract vascular smooth muscle and promote aldosterone synthesis to raise blood pressure [50]. By inhibiting ACE, researchers have been able to cut off the production of angiotensin II and have developed a series of drugs, including captopril, enalapril, and fosinopril, to treat hypertension [51].

Lead compounds discovered from metabolites

Drug metabolism often produces oxidation, reduction, alkylation, demethylation, and binding reactions [52-55]. If a drug's metabolites have pharmacological activities, these metabolites can also be used as drugs or after structural modifications of specific functional groups as lead compounds themselves. The *ad hoc* protection of some functional groups has often led to highly efficacious drugs [56-58]. For example, sulfonamides, highly efficacious lead compounds, have been found in the urine of patients with staphylococcal septicaemia who were treated with prontosil after drug metabolism [59].

Lead compounds found from side effects

When drugs are applied to the human body, the biological activities produced are often diverse. Since drugs are difficult to distribute specifically to target tissues for binding to specific receptors, they have side effects in addition to therapeutic effects [60]. To reduce the side effects of a drug, researchers often carefully observe and systematically study its side effects and metabolism, and then develop new dosage protocols or propose new methods for the drug's use. For example, vinblastine and vincristine compounds were first used as hypoglycemic drugs, but they were subsequently found to also significantly reduce white blood cells [61]. Further studies have found that vinblastine and vincristine are effective in lymphoblastic leukemia transplantation in mice, and thus, these compounds have since become clinical drugs for leukemia treatment [62].

Lead compounds found by computer-aided design

Computer-aided drug design uses computers as a tool to leverage the existing molecular structures and target information of drugs to

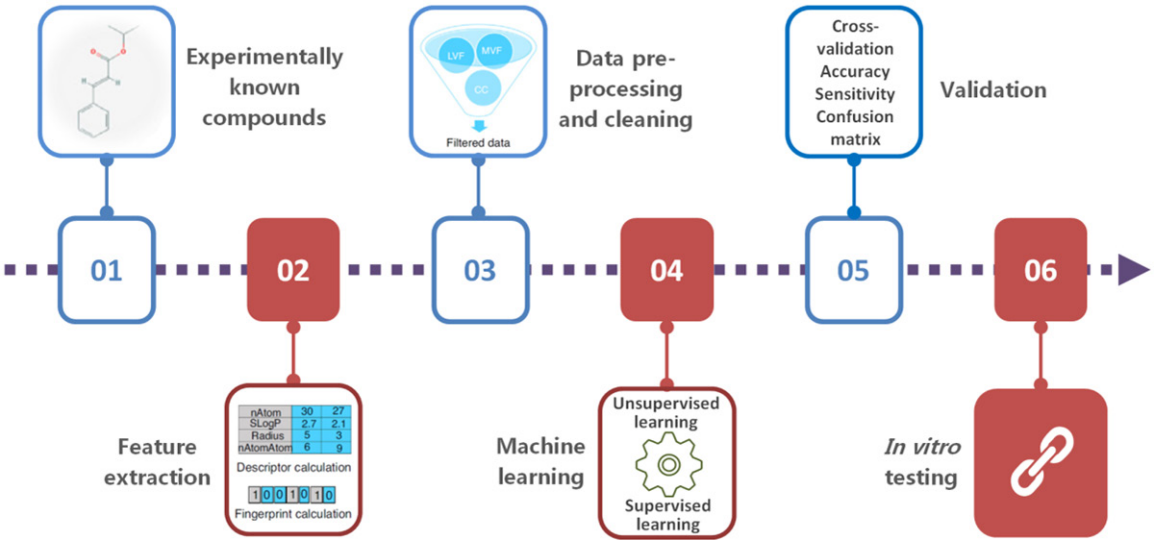

Figure 3. Workflow for machine learning in drug discovery. Over the past decade, Machine learning methods have been recognized as the most important tools for extracting chemical compounds with important biological activities from large chemical databases. To understand the physiological and pathological phenomena, it is important to identify ligands that modulate a particular target activity. The main steps of machine learning comprise data collation, chemical descriptor calculation, classifier/model selection, and model validation.

guide the directional design of small-molecule drugs through theoretical simulations, calculations, and predictions [63-65]. Using a mathematical-combination method, related structural units are sequentially connected in the form of covalent bonds, and a compound molecular library is then established [66]. The molecular library of compounds obtained by combinatorial chemistry is directly used for large-scale screening. This method far exceeds conventional methods in terms of quantity of leads and has incomparable advantages in synthesis speed [67].

Using this highly efficient, minimal, and highly automated combinatorial chemistry and mass-screening technology, it is possible to screen two million to two billion compounds for a particular molecular target in one to two years [68-71]. The combination of computer-assisted drug design and combinatorial chemistry makes screening more accurate, efficient, and convenient than many other methods. This computer-assisted technology has contributed to a major change in the methodology of small-molecule drug discovery, marking the beginning of a new era in the development of small-molecule drugs [72].

ATG4B has been proposed as a drug target. There is increasing evidence that modulation of ATG4B by either si/shRNA-mediated knockdown or the expression of a dominant negative construct yields beneficial results in multiple cancer models, including breast, pancreatic, and lung cancer. Several ATG4B agonists and inhibitors have been described in the literature, identified either by structure-guided molecular docking of compounds in silico, or by screening chemical libraries of compounds with known activity (**Table 1**).

Optimization of lead compounds

After the structure of a lead compound is determined, it is often found to have poor pharmacokinetic properties and/or substantial side effects [73]. These adverse reactions often make lead compounds clinically unusable. Therefore, it is often necessary to optimize the structure of the lead compound to improve biological activity, reduce toxicity, increase specificity, and/or improve pharmacokinetic behavior, in order to improve the drug-forming properties of the lead compound and apply it in the clinical setting [74-77].

The primary strategies for lead compound optimization are as follows: (1) changing the metabolic pathway to improve metabolic stability, (2) structural optimization to reduce toxicity risks in drug design, (3) structural modifications to

Table 1. In vivo models and potential biomarkers for ATG4B inhibition in cancer

Cancer Type	Therapeutic Modality	In Vivo Model	Biomarker
Breast cancer	siRNA ATG4B/Trastuzumab	MCF7 xenograft	HER2, ATG4B
Colorectal cancer	Tioconazole	HCT-116 Xenograft	none
Colorectal cancer	S130/Caloric restriction	HCT-116 Xenograft	none
Colorectal cancer	UAMC2526/oxaliplatin	HT-29 Xenograft	LC3 conversion
Glioblastoma	NSC185058/Chloroquine	M83 glioma xenograft	none
Lung adenocarcinoma	Doxicylcin-inducible ATG4B C74A	GEMM	K-Ras mutation
Osteosarcoma	NSC185058/starvation	SAOS Xenograft	none
Pancreatic ductal adenocarcinoma	Doxicyclin-inducible ATG4B C74A	GEMM	K-Ras mutation
Prostate cancer	ATG4B C74A/doxorubicin	PC-3 Xenograft	none

improve water solubility, (4) promoting the passage of compounds through the blood-brain barrier, (5) reducing cardiac toxicity, and (6) improving plasma stability [78-81].

Prodrug modification strategies

Prodrugs, also known as drug precursors or precursor drugs, are compounds with no pharmacological activity that can be metabolized in the body and converted into substances with specific pharmacological activity [82]. Prodrug design involves improving poor metabolic stability, potential toxicity, low water-solubility, and poor blood-brain barrier permeability in target compounds [83-86]. To solve these prodrug problems, the originating drugs are often connected with non-toxic compounds to form new compounds; a new compound may then improve the shortcomings of the original drug. After a new drug is metabolized in the body, it can be decomposed into the active drug and non-toxic compounds through metabolic processes, such as the action of enzymatic or hydrolysis reactions, to exert its efficacy in the body [87-89].

Prodrug modification strategies usually include esterification, acylation, amidation, and other methods [90]. For example, the oral bioavailability of the antibiotic ampicillin is 40%. Polar carboxyl esterification has been used to obtain the prodrug, pivampicillin, which has increased lipophilicity and an oral bioavailability reaching 95% [91]. Additionally, clinical application of clopidogrel has shown that its cardiotoxicity risk is associated with clopidogrel resistance [92]. A prodrug strategy was used to modify clopidogrel thiolactone, the metabolic intermediate of clopidogrel, to obtain vicagrel. Specifically, vicagrel does not need CYP2C19 to metabolize into the thiolactone form, which can effectively reduce clopidogrel resistance [93-96].

At the same time, the toxicity risk has been shown to be greatly reduced due to the lower effective dose of vicagrel. As another example, a dual Src/Abl inhibitor, pyrazolo[3,4-*d*]pyrimidine derivative, has been shown to have nanomolar-level activity at both Src and Abl enzymatic levels, but its cellular activity is not high, which is probably due to poor water solubility (only 0.05 mg ml^{-1}) [97]. The solubility of an acylated prodrug was 600 times higher, and the corresponding level of cellular activity also significantly improved [98].

A γ-secretase inhibitor and N-methyl dihydropyridine fragment were combined to form a chemical delivery system prodrug. After administration, the 2 h brain concentration reached 345 $ng{\cdot}g^{-1}$, which was about 1.5 times that of the original compound (240 $ng{\cdot}g^{-1}$) [99]. Therefore, prodrug modification by chemical-delivery systems can effectively improve the cerebral permeability of compounds, and increase their intracerebral concentration [100-102].

Strategies for changing a compound's lipid solubility

Most metabolic enzymes in the body have active pockets that bind to lipophilic groups. By reducing a compound's lipophilic properties, the binding activity between compounds and metabolic enzymes is weakened, thus delaying the metabolism of compounds *in vivo* and improving metabolic stability [103-105]. The

anti-thrombin factor Xa inhibitor, developed by the Takeda company of Japan, has a strong inhibitory activity of FXa (IC50 = 28 nmol·L^{-1}) [106]. Although this compound has strong biological activity, it has a very high elimination rate in human liver microsomes, reaching 91.2% [107].

By replacing the seven-membered lactam ring with a six-membered and five-membered lactam ring, the anti-thrombin factor Xa inhibitor has reduced fat solubility, a reduced elimination rate, and an increased activity; when the R group was replaced by a six-member cyclourea group, the obtained compound, TAK-442, had the strongest inhibitory activity and the best metabolic stability of any known anti-thrombin factor Xa derivatives, and is currently being tested in a phase-II clinical study [108].

As another example, a powerful phosphodiesterase inhibitor, PDE4D, developed by Novartis, has a solubility of only 2.3 μg·mL^{-1}, and bioavailability of only 8% in rats due to its large aromatic conjugate region [109, 110]. Researchers succeeded in replacing one of its benzene rings with a cyclohexane or piperidine ring, while removing the other oxadiazole ring and introducing various substituents [111]. The solubility of the resulting compounds improved greatly. PDE4D is an antibacterial drug with good bacteriostatic activity and a strong inhibitory effect on topoisomerase IV [112]. The inhibitory activity (IC50) of hERG is 3 μmol^{-1}. Other compounds were obtained by replacing quinolines with quinolones with greater polarity. The lipid-soluble logD7.4 decreased by 0.6-1.6 units, and hERG inhibition decreased significantly (IC50 > 30 μmol^{-1}) [113]. Through quantitative structure-activity relationship analysis, Levoin has been shown to have a lipid solubility (clogP, clogD, or polar surface area PSA) and aromatic properties that are closely related to hERG inhibitory activity [114]. The fat-soluble aromatic ring in the drug molecule generates a π-π hydrophobic effect with the hERG potassium channel. Reducing liposolubility of molecules, through methods such as introducing electron-withdrawing groups or polar groups on aromatic rings of drug molecules, or replacing benzene rings with heterocyclic rings through bioisosterism, can effectively hinder the hydrophobic effect and reduce hERG-inhibiting activity [115].

Adenosine receptor A2A antagonists can be used to treat Parkinson's disease [116]. The A2A antagonist lead compound reported by Merck (IC50 = 5.5 nmol·L^{-1}) has a good selectivity to adenosine receptor A1 but has strong hERG inhibitory activity (IC50 = 1.5 μmol·L^{-1}) [117]. In terms of useful strategies for liposolubility reduction, compounds a and b were obtained by replacing the end benzene ring with pyrazole, and the lipid-soluble clogP of the resulting compounds decreased by 1.9 and 0.7 units, respectively, whereas hERG inhibitory activity decreased significantly (IC50 > 60 μmol·L^{-1}) while maintaining affinity with A2A receptors and selectivity to A1 receptors [118].

Broad-spectrum antimicrobial agents have good bacteriostatic activity and have a strong inhibitory effect on topoisomerase IV. Their hERG inhibitory activity (IC50) is 3 μmol·L^{-1} [119]. When new compounds were obtained by replacing quinolines with quinolones with greater polarity, lipid-soluble logD7.4 decreased, and hERG inhibitory activity decreased significantly [120].

Bioisosterism strategies

Many compounds contain metabolizable groups. One important strategy to improve metabolic stability, reduce potential toxicity, and improve plasma stability of a compound is the principle of bioisosterism, in which metabolizable groups are replaced with stable bioisosteres [121-123]. The compound 5-(2,8-bis(trifluoromethyl)quinolin-4-yloxymethyl)isoxazole-3-carboxylic acid ethyl ester has activity against *Mycobacterium tuberculosis* (minimum inhibitory concentration [MIC] = 0.9 μmol·L^{-1}), and the compound is prone to being deactivated by CYP catalytic oxidation and ester hydrolysis [124].

To effectively reduce the compound's oxidative metabolic rate, the linking group between quinoline and isoxazole is structurally optimized, containing a trans-double bonded compound [125]. A bioisosterism strategy not only enhances antibacterial activity, but also improves pharmacokinetics. The liver metabolites of nimesulide, especially nitroreductive products, are closely related to nimesulide's toxicity [126]. Aromatic nitrogroup products can be oxidized into quinone imines and electrophilic

products by the P450 enzyme and monoamine oxidase in human liver microbodies [127]. Electrophilic products can further covalently bind to some strong nucleophilic substances (such as proteins and DNA) in the body, which may lead to the production of hepatotoxicity.

In subsequent research on the modification of nimesulide, it was found that arranging the nitrobenzene structure into a pyridine ring structure improved enzymatic activity and selectivity, and also maintained anti-inflammatory activity in rats [128]. The successful application of this strategy avoids aromatic nitro structures and significantly reduces the expected toxicity risk of lead compounds. Novel P2X7 receptor antagonists have been developed by Roche Pharmaceuticals. This lead compound is unstable in human plasma, causing 50% of the prototype drug to be degraded after 4 h of plasma incubation [129]. Therefore, the researchers replaced the urea group in the compound structure with an amide group to obtain a new compound that greatly improved plasma stability while maintaining its inhibitory activity on P2X7 receptors (IC50 = 23 nmol·L^{-1}) [130].

In the process of drug discovery, we often encounter problems with lead compounds, such as poor medicinal properties, poor pharmacokinetic characteristics, toxic effects, and side effects. To improve the drug potency of lead compounds and to accelerate the process of new drug development, structural optimization of lead compounds has become a key link in current drug development [131-134]. Effective approaches to optimize lead compound structure include the rational use of closed metabolic sites, skeleton modifications, reduction of vigilant structural reactivity, chiral changes and methyl strategies to change conformation and increase molecular rigidity to achieve conformational restriction, as well as changing the water-solubility and fat-solubility of lead [135, 136]. The flexible application of the above methods can improve the pharmacokinetic characteristics of lead compounds, prolong the time of drug action *in vivo*, enhance metabolic stability, improve bioavailability, reduce hERG inhibitory activity, reduce adverse effects on the heart, and reduce adverse effects on the liver, kidneys, and other organs [137-139].

Research and development of mimetic small-molecule drugs

Imitative small-molecule drugs are also known as “me-too” drugs. This kind of drug is used to conduct full research on the pharmacological, toxicological, metabolic, and clinical effects and mechanisms of known drugs. Imitative small molecule drugs are then used as the lead compound for structural modifications to obtain new drugs [140-142]. In addition, new chemical entities with the same mechanism of action, or with similar or enhanced effects or certain characteristics, are developed to avoid patent protection of the original drug [143]. This innovative approach to research and develop small-molecule drugs is known as the “me-too” strategy. In small-molecule drug research and development, the “me-too” strategy is carried out from three aspects: bioelectronic-equivalent row replacement, prodrug design, and chiral drug research [144-146].

Replacement with bioelectronic isosteres

The number of electrons in the outermost layer of elements within the same family in the periodic table is equal. Additionally, the physical and chemical properties of elements within the same family are similar to one another. This relationship is extended to atoms, ions, or molecules of equal outer electrons, which are called electron isosteres [147]. When the physical and chemical properties of the atoms, groups, or molecules under consideration are associated with biological activities, groups with similar physical and chemical properties and the same valence bonds capable of producing similar biological activities are called bioisosteres [148-150]. For example, replacing the imidazole ring with a furan ring and thiazole ring yields ranitidine and famotidine, respectively, and the H2 receptor antagonism of these drugs is stronger than that of cimetidine [151]. The use of bioisosteres to replace a group of lead compounds one by one to obtain a series of new compounds is a classic method for pharmaceutical chemists to study drugs [152].

Prodrug design

A prodrug refers to a compound that has little or no activity *in vitro* and releases an active substance after the action of an enzyme or

non-enzyme in the body to ultimately produce a pharmacological effect [153]. For example, lactam antibiotics have a carboxyl group in position 2, and due to strong polarity and acidity, oral absorption is poor [154]. Ampicillin, in the form of ions in the gastrointestinal tract, has a bioavailability of only 20%-30% [155]. Application of a prodrug design to yield pivampicillin, which is obtained by esterification of carboxylic acid, yields increased fat solubility and an improved bioavailability of 95%. Pivampicillin has an *in vivo* antibacterial effect that is two to four times greater than that of ammonia benzyl ester, and yields a high blood drug concentration and short half-life [156]. When carbenicillin is taken orally, it is easy broken down by gastric acid in the stomach, leading to an unstable drug effect. The carboxyl esterification of the side chain to carindacillin yields a drug that is not easily decomposed by gastric acid, and thus can be taken orally, with significant improvement in bioavailability [157].

Chiral drug design

Stereochemistry has occupied a great role in the manufacture and development of pharmaceuticals. Chiral properties play an important role in the determination of pharmacological actions of drugs [158]. In recent years, there has been considerable interest in chiral separation to isolate and examine both enantiomers. For example, the specific drug, omeprazole, developed by Astmzenaca for the treatment of gastric ulcers, is the world's first proton-pump inhibitor that has undergone clinical application [159]. The S atom in the omeprazole molecule is an asymmetric atom. The l-isomer (esomeprazole) obtained through chiral design of the drug has a slow metabolism in the body and is repeatedly generated through internal circulation, leading to a higher blood concentration and longer maintenance time [160-163].

Known small-molecule drug-extension research and development

To shorten development cycles, reduce risks, and improve the success rates of small-molecule drugs, the "new use of old medicine" has attracted increasing attention from researchers [164]. "New use of old medicine" refers to the development of new indications, or new uses, of drugs that have been marketed for other purposes previously [165]. Owing to the detailed pharmacokinetics and safety data of drugs already on the market, the development of new applications can be quickly evaluated in phase-II clinical trials, which can save approximately 40% on the costs of research and development and can shorten the development cycle [166-168]. For example, aspirin has expanded from a conventional anti-inflammatory analgesic to a small-molecule drug that can dilute blood, prevent thrombosis, and reduce the incidence of stroke [169]. The original methoxypyrimidine, for the treatment of pneumonia, was approved for the treatment of AIDS [170].

The pregnancy drug mifepristone has since been approved for severe psychiatric depression. Thalidomide is a synthetic glutamic acid derivative that was once called a reaction stop, and has a calming and antiemetic effect [171]. In 1998, thalidomide was approved by the FDA for the treatment of ENL. In 2006, the FDA approved its combination with dexamethasone for the treatment of multiple myeloma (MM) [172]. Metformin, a biguanide compound from *Galega officinalis*, has been used to treat hyperglycemia since the 1950s and is one of the most widely prescribed diabetic drugs. Numerous studies have shown that metformin, in addition to being used in the treatment of diabetes, can also be used to treat off-label diseases such as polycystic ovary syndrome, nonalcoholic steatohepatitis, and HIV-related metabolic abnormalities [173].

In tumor therapy, the mechanism of metformin is becoming increasingly clear, and the application of metformin in the field of non-diabetic diseases is increasing. A series of promising early clinical trials are underway, making it highly likely that this classic drug will be turned into a novel anticancer drug [174].

New technology for small-molecule drug discovery

Drug discovery in the 1960s and 1970s relied primarily on cell and animal models that mostly used phenotypic screenings [175-177]. After entering the 21st century, with the rapid development of computational biology, bioinformatics, molecular biology, and chemical biology, the molecular targets of small-molecule drugs have since been elucidated [175-177]. The Nikolovska-Coleska lab conducted a high

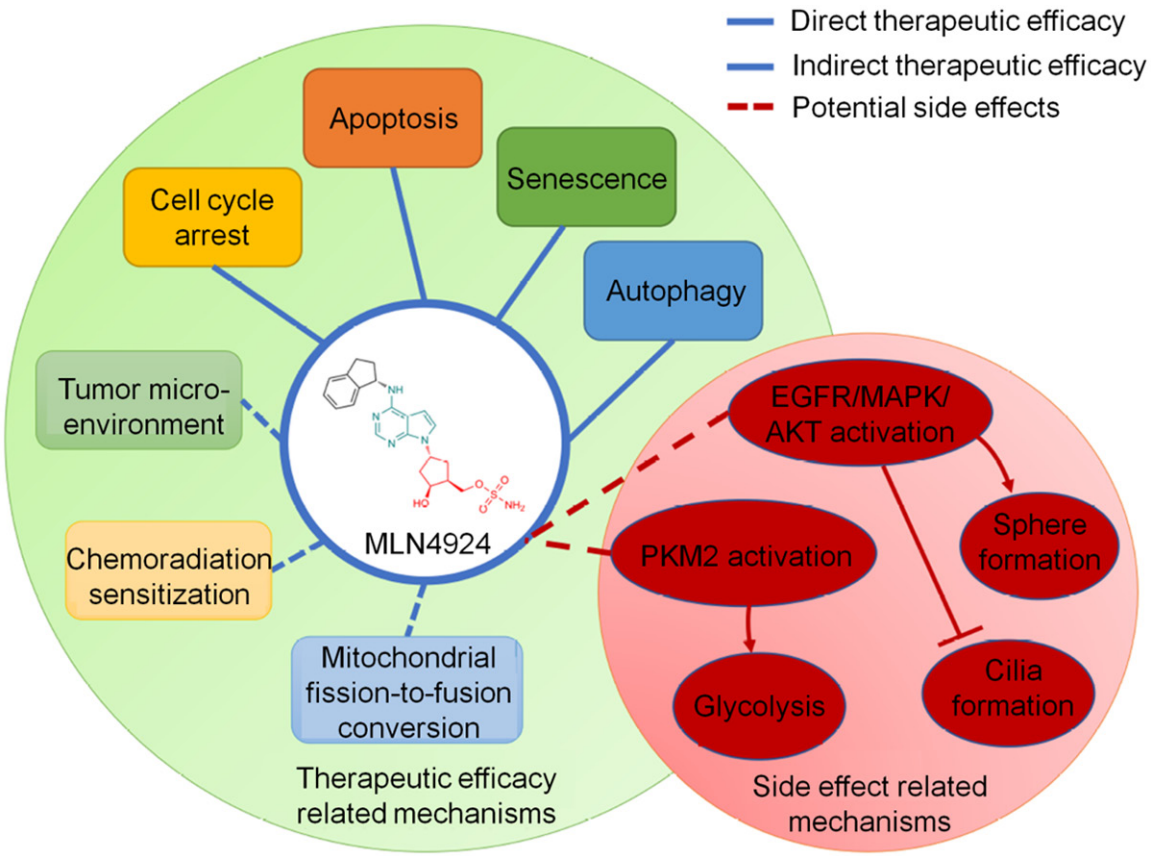

Figure 4. The first-in-class NAE inhibitor, MLN4924. A scheme of the mechanisms of MLN4924 regarding to its therapeutic efficacy and side effect.

throughput screening (HTS) campaign with a library of 53,000 synthetic small molecules to identify Mcl-1 inhibitors, which led to the identification of UMI-59 (Ki = 1.55 μM). This molecule inhibited Mcl-1/Bid interaction and displayed greater selectivity toward Mcl-1 compared to other Bcl-2 proteins in the FP assay. Additionally, the genome project and proteome project are new approaches for drug design. The application of computational biology, bioinformatics, molecular biology, and chemical biology makes it more efficient to discover novel targets for drug action [178].

Methods such as selecting targets for important diseases, designing lead compounds, and optimizing lead structures using combinatorial chemistry and high-throughput screening methods have recently been developed [179-181]. In 2009, the discovery and subsequent clinical trials of an NAE inhibitor, MLN4924 (pevonedistat), set a milestone that validated the neddylation pathway as an effective anticancer target. Thereafter, there has been continuous effort to seek more neddylation inhibitors.

Now, a decade later, high-throughput screening, virtual screening, as well as structural-based design have yielded a diverse collection of small-molecule inhibitors of neddylation, and some have shown promising anticancer activities (**Figure 4**). Therefore, high-throughput screening, virtual screening, structure-based drug design, and optimization of lead compounds have become common techniques for small-molecule drug discovery.

Outlook

In conclusion, the creation of novel structures and biologically active drugs via the basic pathways of small-molecule drug discovery and the instant identification of new chemical entities (NCEs) are highly respected and lucrative approaches in the medical community. However, this kind of small-molecule drug research

is difficult to develop, and the risks are often great. Further research and development of known drugs can extend to small-molecule drug research and development. In the establishment of a compound library, high-throughput screening based on a certain molecular target can obtain the complex crystal structure of small molecules and target proteins, and many classic drugs can be exploited to have novel uses for the treatment of other diseases and disorders. Once life science enters the post-genomic era, scientists will be able to find and discover new genes from a large number of gene-sequencing results and deeply study their functions and regulatory networks. Such an approach will further improve the quality and efficiency of innovative drug research through a large number of bioinformational databases, compound-information databases, biochips, and other high-tech technologies. However, human biology is so complex that drug discovery has not been as efficient as might be expected. The cost and efficiency of clinical trials are rate-limiting steps in drug discovery. Due to these factors, the significance of new technologies in drug discovery can be leveraged in terms of the following three strategies: (1) if a drug target is correct, find the most effective regulation mode and molecule; (2) demonstrate the effectiveness of the target as early as possible; and (3) take advantage of the fact that effective drugs can be found even when a clear target is not identified.

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Disclosure of conflict of interest

None.

Address correspondence to: Da Fu, Central Laboratory for Medical Research, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 36 Yunxin Road, Shanghai 200072, China. E-mail: fu800da900@126.com; Kai-Jian Chu, Department of Biliary Tract Surgery I, Third Affiliated Hospital of Second Military Medical University, 225 Changhai Road, Shanghai 200438, China. E-mail: lingbei51@aliyun.com; Ji-Bin Liu, Cancer Institute, Nantong Tumor Hospital, West 48 Qingnian Road, Nantong 226631, China. E-mail: tians2008@163.com

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