Review

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Future Medicinal Chemistry

An overview of drug discovery and development

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A new medicine will take an average of 10–15 years and more than US$2 billion before it can reach the pharmacy shelf. Traditionally, drug discovery relied on natural products as the main source of new drug entities, but was later shifted toward high-throughput synthesis and combinatorial chemistry-based development. New technologies such as ultra-high-throughput drug screening and artificial intelligence are being heavily employed to reduce the cost and the time of early drug discovery, but they remain relatively unchanged. However, are there other potentially faster and cheaper means of drug discovery? Is drug repurposing a viable alternative? In this review, we discuss the different means of drug discovery including their advantages and disadvantages.

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Drug discovery is a costly process that takes on average more than a decade from discovery to approval. Notably, the associated cost and approval time is different depending on the drug that is being discovered and the targeted disease. For instance, the review process for drugs that offer only minor improvements over existing marketed therapies will be much longer than an urgently needed drug that would usually go through a priority review process [1]. Also, the overall cost of developing an orphan drug (a drug that treats rare and neglected medical conditions) is much lower than the cost of a nonorphan drug [2]. For example the estimated drug development cost of fexinidazole, approved to treat sleeping sickness a neglected disease, was EUR 55 million [3], which is significantly lower than the nonorphan drug development cost that is estimated to exceed US$2 billion [4].

However, current advance technologies not only hastened the discovery process, but also working to enable the development of personalized therapeutics. Traditionally, drug discovery utilizes whole plant extracts driven by single compound-based medicine. While this led to the discovery of many successful therapeutics, often these procedures accompanied by several challenges that may result in unacceptable biopharmaceutical or pharmaceutical performance, poor targeting or formulation limits [5]. The high associated costs and slow processes make these procedures unsustainable and deemed impractical and hence, discarded by modern medicine strategies.

Thus, industrial research and development (R&D) are continuously searching for new methodologies to speed up the discovery and are constantly assessing new technologies and applications from other research areas. However, identification of a robust and viable lead drug from the hit stage to drug candidate remains a challenge that the pharmaceutical industry is trying to overcome.

Consequently, drug discovery has witnessed rapid changes that over the last few decades produced significant advances in scientific research and technological innovation that enabled the generation of novel drug candidates and rapid translation to usable entities. The availability to develop therapeutic agents targeted at a particular protein or biological activity in a living cell has revolutionized drug discovery. In addition, the establishment of high throughput at different stages of drug discovery and development, and technological advances such as the sequencing of the human genome have contributed greatly to the transformation of the process.

Noteworthy, the development of high-throughput screening (HTS), and small-molecule drug libraries have contributed to the establishment of the new era of drug discovery. Current cutting-edge technologies enabled the industry to perform HTS and ultra-high-throughput screening (uHTS) campaigns of large combichem libraries

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Table 1. Examples of currently used drugs and their sources.

Drug	Use	Source	Ref.
Digitalis	Antiarrhythmic	Natural: *Digitalis* leaf	[19]
Penicillin	Antibiotic	Natural: fungal	[20]
Captopril	Antihypertensive	Natural: Bothrops jararaca snake	[21]
Ceftaroline fosamil	Antibacterial	Natural: fungal, *Acremonium chrysogenum*	[28]
Capsaicin	Analgesic	Natural: *Capsicum* fruits	[29]
Romidepsin	Anticancer	Natural: bacteria, *Chromobacterium violaceum*	[30]
Amoxycillin	Antibiotic	Semi-synthetic	[13]
Paclitaxel	Anticancer	Semi-synthetic	[23]
Aripiprazole	Antipsychotic	Small molecule	[31]
Esomeprazole	Gastroesophageal reflux disease, Zollinger–Ellison syndrome, stomach ulcers	Small molecule	[32]
Rosuvastatin	Cardiovascular diseases	Small molecule	[33]
Sofosbuvir	Antiviral	Small molecule	[34]
Bortezomib	Anticancer	Small molecule	[22]
Interleukin-2	Anticancer	Biological	[24]
Rituximab	Autoimmune/cancer	Biological	[25]
Cetuximab	Anticancer	Biological	[35]
Etanercept	Autoimmune	Biological	[36]
Palivizumab	Antiviral	Biological	[37]
Ritonavir	Anti-HIV infection	Computer-aided design	[26]
Oseltamivir	Anti-Influenza	Computer-aided design	[27]
Dorzolamide	Glaucoma and ocular hypertension treatment	Computer-aided design	[38]
Epalrestat	Diabetic neuropathy	Computer-aided design	[39]
Isoniazid	Antituberculous	Computer-aided design	[40]

The table lists randomly selected examples of currently approved medicines and their source of origin.

on purified biological targets [6]. These have reduced the time required for the initial drug screening and hit to lead screening periods.

However, important parameters that usually result in late lead failure, such as efficacy and toxicity remain a challenge in the drug discovery sector. One important variable that we hypothesized to have an effect on lead outcome is drug source, for example, natural or synthetic. There are no data available about the relationship between drug source and rate of success or failure. Hence, is there a relationship between the drug source and lead failure rate? Are drugs of natural sources less toxic than synthetic? Are synthetic drugs more effective than natural extracts? Thus, the current manuscript briefly discusses the different and most commonly used drug sources and draws a comparison between them.

Natural sources

- Medicinal plants represent a rich source for drug discovery;
- They have wide and diverse chemical structures;
- Many therapeutic agents are based on natural products;
- The challenges in purification and characterization of natural products limit their usage in drug discovery.

Medicinal plants have always been and still are a valuable source of therapeutic agents. There are several effective therapeutics of natural sources widely used today. Table 1 lists examples of licensed therapeutics including their source and use. Historically, drug discovery relied solely on natural products as the primary source of medicines that has significantly influenced the advances in biology and inspired drug discovery and development. Natural-drugs or naturally derived drugs are those that contain pharmacologically active ingredients derived from biological or mineral sources and intended for use in the diagnosis, cure, mitigation and prevention of diseases [7]. Evidently, several pathologies were reported to have been successfully treated with natural or naturally derived medicines. Traditionally, natural medicines were extensively used both as concoctions or concentrated plant extracts without

isolation of active compounds [8], but advances in experimental procedures in the nineteenth century enabled the isolation and purification of active principles from these plants. Nevertheless, natural products have been the single most productive source of leads for the development of drugs [9].

The structural diversities of natural products and the plentiful scaffolds serve as an important basis for the generation of new compound library design [10]. Also, the diverse chemical structures of natural products still the best source of drugs and drug leads that inspires the production of various semisynthetic agents, which are a mixture of synthetic and natural sources generated via converting natural materials into end products by chemical reactions [11,12]. An example of semisynthetic agent is amoxycillin (α-amino-*p*-hydroxybenzylpenicillin), which is a semi-synthetic broad spectrum penicillin [13].

Despite the potentials that natural products may have, pharmaceutical companies appear to significantly scale back or reduce natural product programs because of the remarkable advances in combinatorial synthesis and HTS that consequently enabled the generation of a vast number of synthetic small-molecule libraries [14]. The declining number of natural product discovery programs, does not seem to affect the number of approved natural drugs, as it has recently been estimated that the structural origins of approximately half of all newly approved drugs can be traced to a natural product [9].

Natural products enabled the identification of many chemical leads for the development of various disease treatments, and despite the reduction or elimination of the in-house natural product groups by most pharmaceutical companies in the USA, there seems to be a renewed interest in natural products as a reliable source for new chemical entities.

In fact, some argue that the interest in natural products as a potential source of drug discovery will likely to resurface again. Their argument is partly driven by the failure of other drug discovery methods of finding new drug leads in major and crucial therapeutic areas such as metabolic diseases, immunosuppression and anti-infective [15]. The recent development of high-throughput platforms amenable for discovery and development of natural therapeutic products may also contribute to the growing interest in natural products [16]. Several hundreds of natural-product or natural-derived compounds are being investigated in clinical trials and at least a 100 similar projects are in preclinical development that have been derived from plants and microbial sources [17,18]. However, there are several drawbacks associated with natural product drug discovery including the difficulty with chemical purification and characterization, as well as the challenges in chemically modifying the complex natural product scaffolds [17].

Interestingly, the results of principal component analysis of the chemical, structural and physicochemical properties of drugs from natural sources compared with drugs of synthetic origins approved between 1981 and 2010, showed that drugs of natural origins have greater chemical diversity, and interrogate larger regions of chemical space than drugs of synthetic origins [9].

Small molecule library & HTS

- Drug screening using small molecule libraries is widely used in the pharmaceutical industry;
- Small molecules are typically compounds less than 500 in molecular weight;
- High-throughput drug screening model systematically screen thousands of small molecular compounds against a biological target;
- High content screen is another model of HTS that simultaneously monitor and analyze cellular responses to an investigational drug.

The advancement of science and technology aided the shift of drug discovery focus from the traditional drug discovery process such as the use of medicinal plants to small molecule synthesis, which thought to be easily synthesized, with relative chemical stability and simple characterization of reactivity [41].

Typically, a small molecule screen is a process where hundreds or thousands of molecules, less than 500 in molecular weight, systematically screened against a biological target [6]. The procedure is widely used by the pharmaceutical industry where different biological libraries are generated and analyzed in high numbers using HTS. The goal of the procedure is to detect molecules that modulate a particular biological process, and hence, can be developed into a drug lead. This would allow the pharmaceutical industry to produce large-scale molecules at low costs.

Furthermore, HTS have become the standard method for discovering new drug leads for different human diseases [42,43]. It is an automated process of testing large numbers of chemical or biological compounds against

specific targets. They represent an important drug screening methodology that is commonly used in the early stages of drug discovery to identify potential hits. While the methodologies do not necessarily identify lead compounds, they are an important means of detecting potential hits that can possibly be further optimized, thus, providing the starting point in drug discovery [43].

Conventionally, HTS are associated closely with small molecule drug libraries and relied mainly on microtiter plate-based culturing with a spectroscopic readout for product titer [44], which typically have the potential to screen less than 10,000 compounds per day. However, the technological advancement have resulted in the development of uHTS that can perform in excess of 100,000 assays per day as well as newer, more sensitive and large scale systems with faster turnout readings than the traditional strategy [44,45].

One of the most commonly used HTS screening models is the cell culture based methods, which can provide considerable amount of biological information during a drug screen [46]. A carefully designed culture-based HTS model should have high sensitivity with low signal-to-noise ratio, to be cost effective, easily executed and in at least micro-scale format amenable to translate to production scale. Typically, HTS are performed in 96-well microplate format and utilize liquid-dispensing and plate-handling robotics for automation, but in an effort to speed up the discovery process, many are adopting 384-well plates and larger [45]. However, the adaptation or the format of the screening (96, 384 or 768) will depend on the type of screening, the target and the assay used. For example in cell proliferation assays where the endpoint of the screen is to measure tumor growth or growth inhibition will not be suitable in 768-microplate, as it is impossible to mimic the biological processes in small-scale models [47], but are widely used for other biological testing including antimicrobial screens [43].

Cell culture-based assays are also extensively used in high-content screening (HCS), where automated images and data analyses are combined to monitor live cell responses during high-throughput compound screening to identify drug targets or new lead compounds [48].

Generally, HCS are more informative than the classical HTS that are typically analyzed using a plate-reader. The use of HCS enables the monitoring of multiple biochemical and morphological parameters simultaneously [49]. Nevertheless, one of the main drawbacks of HCS is the extraction of relevant information from the large amount of data typically generated from image analyses [50].

Limited screen/targets, is considered as one of the main disadvantages associated with small molecule library. It has been reported that small molecule drugs address a limited range of targets. For instance, Overington *et al.* 2006, estimated that approved small-molecule drugs target to be no more than 207 proteins encoded by the human genome with 50% target four protein classes only (nuclear receptors, rhodopsin-like G-protein coupled receptors, voltage-gated ion channels and ligand-gated ion channels) [51]. This finding is further supported by Santos *et al.* 2017, which claimed that 70% of the approved small-molecule drugs target four human protein targets; 33% target Rhodopsin-like G protein-coupled receptors, 18% target ion channels, 3% act on kinases and 16% target nuclear receptors [52]. This might be due to the fact that most of these libraries are based on the 'drug-like' structures with certain boundaries and physicochemical parameters [9].

Computer-aided drug design methods

- Computer aided drug design (CADD) involves structure and ligand-based discovery;
- The method evaluates different biological target properties and provides novel compound design suitable to interact with the target;
- CADD is capable of predicting important parameters including blood–brain barrier.

CADD approach considerably accelerated the discovery time and reduced the cost of drug discovery [53]. CADD utilizes two methodological approaches, structure-based and ligand-based methods. The structure-based method analyzes the structure of biological targets and identifies the key sites that are crucial for biological functions [54]. The computer will then assist in designing compounds capable of interacting with the identified target to affect its biological function [55,56]. However, the ligand-based method, evaluates the physiochemical properties and activities of known ligands, and then provides different designs of novel compounds with desired activities [55,57], which is rather a useful method especially when the information of a biological target is limited or absent [54]. Table 1 shows some examples of CADD designed and developed US FDA approved drugs.

Generally, CADD uses construction algorithms that allow the designing of novel compounds with high probability of being highly active, readily synthesizable and avoiding undesirable properties such as poor ADMET (absorption, distribution, metabolism, excretion and toxicity) [53,55], and can be applied during different stages

of the drug development process. For instance, it can be used prior performing HTS to filter potentially active compounds in large libraries (virtual screening), thus reducing the number of compounds to be synthesized and tested [58]. This will considerably reduce testing time, workload, experimental use of animals for *in vivo* testing and thus expenditure [55]. In addition, CADD can detect drug safety, efficacy and poor ADMET, which are the main reasons of drug withdrawals from clinical trials and the cause of high attrition rates [59]. Thus, CADD tools can reveal the optimization options for the lead compound, hence leading to an improved ADMET outcome, increases drug's potential efficacy and decreases potential toxicity [58,60].

Furthermore, recent adaptation of deep learning in CADD has improved the prediction of several parameters particularly, drugs that act on the central nervous system as well as detecting the permeability of blood–brain barrier, which poses a serious challenge in drug development [61]. Constant advancements in computational technologies and biological understanding rapidly eliminate the present limitations of CADD approach, making it a valuable tool in drug development [56,58]. An interesting application of CADD is in drug repurposing/repositioning. Although it is a relatively new direction with numerous limitations and potential obstacles, several drugs have already been repurposed or indicated for repurposing using CADD tools [56,60,62].

One of the major drawbacks of CADD is that it provides a design for a molecule that will fit into a particular structure, but does not necessarily detect the activity in the biological system as a whole, as it is quite complex and controlled by different parameters.

Biological sources

- Biological agents have been successfully used for many years;
- There is a continual increase in the approval of biological agents, making them the fastest growing therapeutic class;
- There several limitations associated with biological agents including their large and complex structure as well as their high price.

An interesting source of drugs that is currently the focus of many pharmaceutical companies is biological drug candidates. Although not entirely new, biological therapies have been widely used for many years, for example, in the development of human growth hormone and insulin [63]. However, increase in the knowledge of genetics and cell processes resulted in the dramatic increase in targets for biological therapies.

In comparison to classical small-molecule screening, there is a more steady increase in the approval of biological therapies to that of the small-molecule drugs. In 2015, Stratton *et al.* reported a significant increase in the biological drug approval over the last 30 years including monoclonal antibodies and vaccines as well as a continual decline in the small-molecule drug counterpart [9].

They are one of the fastest growing therapeutic classes, swiftly overtaking the growth of small-molecule drugs with recent reports claimed that the sale of biological therapies had significantly increased to more than 25% of the total market sale with a value of more than USD $232 billion [63].

Biological drugs have the ability to reach targets that are considered 'undruggable'. For example, stabilized peptide therapeutics could potentially reach undruggable targets, significantly increasing the potential druggable genome [64].

The disadvantages for this class is based on some of their characteristics such as their large and complex structures that require extensive analytical data as well as their high price. Also, biologics require special handling as they are often less stable than chemically derived drugs as well as requiring controlled temperature and light, and protection from jostling when in its liquid form [65]. However, the continual advances in the biological technology will improve biological production, effectiveness and the overall costs.

Drug repurposing

- Drug repurposing is finding new therapeutic uses for approved drugs;
- The process aims to overcome certain constrains associated with other forms of drug discovery such as time, financial and attrition rate;
- There is a lack of intellectual property laws to protect drug repurposing.

The slow pace of new drug development, the high associated cost and the high rate of late-stage failures make repurposing/repositioning of 'old' drugs a very appealing and more cost effective alternative. Drug repurposing is

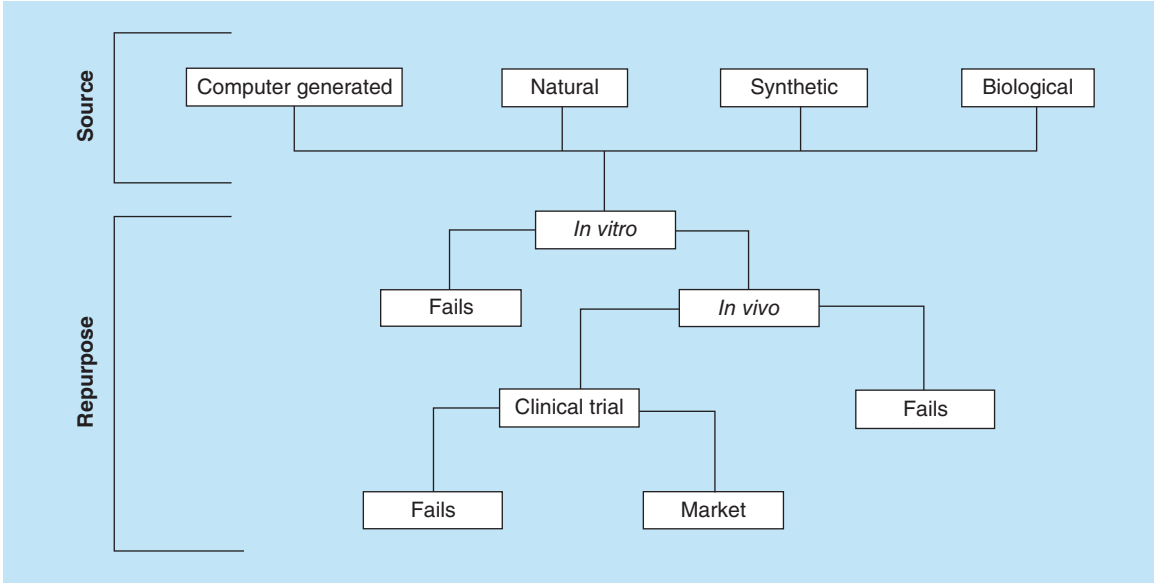

Figure 1. A summary of drug discovery and development. Diagram summarizes the typical pathway of a new drug entity, starting from its source through to different screening stages. Diagram also illustrates the timeline of drug repurposing.

a process of finding new therapeutic indications for low risk marketed drugs, which could potentially reduce the drug developmental time and the associated costs [66]. In comparison to the conventional drug discovery using biological testing approaches, drug repurposing has much lower costs and significantly fewer barriers [57].

Drug repurposing is not an uncommon drug discovery approach that aims to discover new therapeutic benefits of existing drugs rather than searching for entirely new therapeutic agents. The approach is increasingly used to overcome limitations of financial support, timeline and resources constrains that usually occur during traditional drug discovery [67]. The accessibility of advance knowledge and genomic databases have further encouraged the rapid development of novel computational approaches [68].

A drug may be repurposed during any stage of its development (Figure 1). For instance, sildenafil was trailed for the treatment of hypertension, but was then indicated for the management of erectile dysfunction [69]. Other examples include the antidiabetic drug metformin, which is prescribed off-label for the treatment of polycystic ovary syndrome (PCOS) [70,71], antiviral activity of calcium channel blockers, gliotoxin [72–74], as well as the antifungal itraconazole, which was found to have anticancer activity [75]. Other therapeutics such as herbal products also have the potential for repurposing for example, the antifungal meltefosine has shown anti-leishmanisis activity in balb/c mice [67].

However, from a commercial point of view, drug repurposing might not be as attractive as other means, this is because the intellectual property (IP) laws that govern drug repurposing is limited [57]. This is due to the fact that most of the novel drug target disease associations are likely confirmed by publications or online databases; thus, according to the law, it is difficult to seek IP protection for such associations [68].

Conclusion

Traditional drug discovery approaches are unsustainable due to the high associated cost, failure-potential and process time. There is a great effort by industry to speed up the drug discovery process to find new therapeutics as well as discovery approaches. The technological advances in different medicinal areas enabled the pharmaceutical industry to employ different approaches in a hope to hasten the discovery process. Despite these efforts, the drug discovery process remains a lengthy and highly expensive venture. Drug screening, regardless of the source, synthetic small-molecule or natural source, does not reduce the likelihood of late lead failure. An alternative less risky option to biological screening is drug repurposing, which is safer, cheaper and may be a lot quicker than traditional screening, but is also less profitable for non-IP holders. Therefore, to reduce the cost, the potential rate of failure

and to speed up the discovery process, there needs to be a form of incentive for the pharmaceutical industry and non-IP holders to screen licensed drugs against other targets.

Future perspective

We anticipate that over the next decade, new and evolving technologies would contribute to the development of new chemical entities and significantly improve structural diversity of synthetic libraries. The impact of the new technologies, particularly artificial intelligence, would most likely improve the time of drug discovery and the risk of late-stage failure by providing early prediction about new chemical and biological targets. Such predictions would also have a significant impact on drug repurposing by identifying novel therapeutic indications.

Financial & competing interests disclosure

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