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Multidisciplinary science for drug development

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Abstract

This Article Provide a brief overview of the processes of drug discovery and development. Our aim is to help scientists whose research may be relevant to drug discovery and development to frame their research report in a way that appropriately places their finding within the discovery and development process and thereby support effective translation of preclinical research to humans. One overall theme of our article is that the process is sufficiently long, complex, and expensive so that many biological targets must be considered for every new medicine eventually approved for clinical use and new research tools may be needed to investigate each new target. Studies that contribute to solving any of the many scientific and operational issues involved in the development process can improve the efficiency of the process. An awareness of these issues allows the early implementation of measures to increase the opportunity for success. As editors of the journal, we encourage submission of research reports that provide data relevant to the issues presented. New drugs are continually required by the healthcare system to address unmet medical needs across diverse therapeutic areas, and pharmaceutical industries primarily strive to deliver new drugs to the market through the complex activities of drug discovery and development. This involves identifying and validating lead compounds that can bind to a target.

Introduction

Drug discovery has a long history and dates back to the early days of human civilization. In those ancient times, treatments were often discovered by chance or resulted from observation of nature, typically but not exclusively, using ingredients extracted from plants/ animals , and not just used for physical remedy but also for spiritual healing. Modern drug discovery research started to being performed around the early 1900s. Nowadays, the development of a new medicine usually starts when basic research, often performed in academia, identifies a macromolecule (i.e. a molecule with a large molecular weight lie genes/proteins), or a dysfunctional signaling pathway or a molecular mechanism apparently linked to a disease condition (pre-discovery stage). In general, at this stage, research teams attempt to identify the so-called therapeutic targets (often a protein) that are linked to

the disease state. To be nominated therapeutic target, scientists will also have to find therapeutic agents that modify the function of the perturbed target and restore health or alleviate symptoms. Finding the right target is however extremely challenging. Further, drugs are efficient in humans because of specific actions on the intended therapeutic target but also due to interactions with other, unintended (often unknown) targets! The process continues with the search of therapeutic agents followed by a preclinical phase, during which potential drugs are tested in a battery of animal models, to demonstrate safety and select drug candidates novel strategies to avoid animal testing are being developed, see below). Clinical studies in humans can then get started to establish safety and efficacy of the drugs in patients with the highest benefit- to-risk ratio). The studies are then submitted to regulatory agencies, which review the documents and decide about market approval. If the review is positive, the drug can then be released to the market and be administrated to patients. Once a drug has been approved, investigations continue to monitor putative side effects that could be caused, over time, by the new treatment. This last step is often referred to as pharmacovigilance studies (or real-world evidence), generally dubbed “phase 4” clinical trial. The entire drug discovery and development process involves many disciplines, years of efforts and is very expensive. It also implies the generation and use of vast amount of data usually obtained via different types of high-throughput technologies. Many of these experiments and the analysis of the results can be automated via computer-assisted methods to speed-up some steps of the process, gain knowledge and reduce mistakes.

Drug discovery consists of 5 major steps, including a few subdivisions in each of them:

1. Pre discovery

2. Pre-clinical research

3. Clinical research

4. Post-marketing surveillance

Today Indian pharmaceutical industry is ranked 3rd in terms of generic discovery of drugs in a large volume due to development in the field of chemistry and collaborative research and development with other drug agencies for multi- disciplinary outcomes. The following phases of drug discovery need to be understood in detail in order to know the drug discovery and development process.

Pre-clinical research

When a suitable drug candidate has been found, the next step is to carry out in vivo testing of the drug candidates to ensure its safety and efficacy using pre-clinical studies. This particularly involves testing on laboratory animal species like rats, mice, rabbits, monkeys, and guinea pigs to test the appropriate benefits and mechanism of action, routes of administration, dosage, adverse drug events, non- targeted interactions, comparison of efficacy, etc [26]. It ensures that the drug is sufficiently safe to be tested on humans; it enlightens the clarity if there is any effect of the selected drug on gender, particular age group, race, or other ethnic groups. Thus, pre-clinical research can be done to know the toxicity, pharmacokinetics and efficacy of a new drug entity before experimenting on humans [26, 27]. It gives a preliminary idea regarding the behavior of drug.

Clinical research

Before a drug is approved by the regulatory authority, it has to undergo extensive clinical trials that have been divided into few phases where each phase has its own relevance. Clinical trial is basically done to know whether a new drug in the verge of getting developed actually works or is it safe for the people. This research can be helpful in estimating the disease diagnosis, extent of a disease, detection, safety and presence of any side effects related to the drug. For this purpose, healthy volunteers from various regions are selected and trial is conducted on them to answer the questions regarding the disease and the drug profile. Before the clinical study is actually started, an application to conduct the research on a particular drug needs to be submitted to the Central Drugs Standard Control Organization (CDSCO) for approval. This application is known as Investigational New Drug (IND) application which contains results from pre-clinical studies, drug information, outline or study protocol to be carried out, and details about the research team who will be responsible for carrying out the trials.

Phase-0

This is done to know whether the drug does what it is expected to do. This also helps to save a huge amount of time and money. Here, micro-dosing of a drug is given, due to which risk factors are not there, and as a result, a drug can be tracked if it is reaching the site of action where it is desired, whether it is acting in a positive

way and how the body reacts to it. Not every drug undergoes this trial, and it is conducted with a very limited no. of people for a short period of time.

Phase-I

This is the first step in clinical trial where less than 100 volunteers are involved, may be around 20-80 people. Drug is given to check the safety dose and the maximum tolerable dose of a drug up to which it does not show any considerable side effect, here safety is the main concern and studying the response of a disease is not the main motive.

Phase-II

Here the disease response is studied in around 25-100 volunteers and a comparative high dose is given as compared to the previous phase of trial. Efficacy is the main concern of this study, if majority of the patients are showing response with minimal
side effects, then the drug may proceed towards the phase-III clinical trial.

Phase-III

In this phase, comparative evaluation is done with the already established drug of similar category to assess the safety and efficacy of the developed drug. Here the volunteers are assigned to random groups and they himself including the physician are not aware of the specific group in which they are placed (double-blinded) . It involves a large no. of people, among thousands from different geographical regions or countries and the tests are conducted for a long time period. Placebo groups are also included in this study to compare the standard and the test drug. If a patient experiences serious side effects which are less likely to be manageable, the treatment is stopped immediately and care as given . All the parameters for sample collection, treatment and particulars should be stringent and followed with proper skill and knowledge

Post marketing surveillance-Phase-IV

Is there still something remaining to be known about the drug? The answer to this question is yes. Whenever a new drug candidate is introduced into the market, it contains a lot of questions that needs to be addressed. Whether it shows any rare side effect that was not observed before, does it improves the quality of life when taken for a long period of time, can all groups of people regardless of being wealthy or poor can have an access to this drug . All this things needs to be questioned and answered at the same time which is only possible if the drug is reaching to the population affected with a cause. It can help future patients to increase the reliability on a drug. Thus, it is a post

marketing surveillance study and marks the final process of clinical research after which the drug is free to be used without any hindrance.

Objectives and Purpose of Drug Discovery

The purpose of drug discovery and development research is to identify and characterize molecules with the potential to safely treat diseases by developing new drugs that are both effective and well-tolerated, ultimately aiming to improve patient lives by providing new therapeutic options for unmet medical needs; this involves a multi-step process including target identification, lead compound discovery, optimization, preclinical testing, and clinical trials to bring a safe and efficacious drug to market.

Key objectives of drug discovery and development research include:

1. **Identifying a disease target:** Understanding the molecular mechanisms underlying a disease to pinpoint specific proteins or pathways that can be targeted by a drug.
2. **Lead compound identification:** Screening large libraries of chemical compounds to find molecules that interact with the chosen target and exhibit desired biological activity.
3. **Lead optimization:** Modifying the chemical structure of a lead compound to improve its potency, selectivity, and pharmacokinetic properties (absorption, distribution, metabolism, and excretion).
4. **Preclinical testing:** Evaluating the safety and efficacy of potential drug candidates in animal models to assess their therapeutic potential and identify potential toxicities.
5. **Clinical trials:** Conducting human studies in different phases to evaluate the safety and efficacy of the drug in various patient populations, determining the appropriate dosage and treatment regimen.
6. **Regulatory approval:** Submitting comprehensive data to regulatory agencies to gain approval for marketing and distribution of the new drug.

Important aspects of drug discovery and development research:

Target validation: Confirming that the chosen molecular target is directly involved in disease pathogenesis.

Structure-activity relationship (SAR): Studying how changes in the chemical structure of a compound affect its biological activity.

High-throughput screening (HTS): Utilizing automated systems to rapidly screen large compound libraries against a target

Drug delivery systems: Designing methods to efficiently deliver drugs to the desired site of action in the body.

Pharmacokinetics (PK) and pharmacodynamics (PD): Studying how a drug is absorbed, distributed, metabolized, and excreted within the body, and how it interacts with its ta

Strategies for improved success in the drug discovery and development process

Key approaches

Several strategic approaches to enhance efficiency in the drug discovery and development process have been proposed, adopted, and exploited to varied extent in the pharmaceutical research and development (R&D) projects. They include exploitation of genomics and proteomics, the complementarity of phenotypic and target-based screening platforms, expanding the use of existing drug molecules through repurposing and repositioning, use of collaborative research, exploring under-served therapeutic areas, outsourcing approach, and pharmaceutical modeling and artificial intelligence.

Exploitation of genomics and proteomics

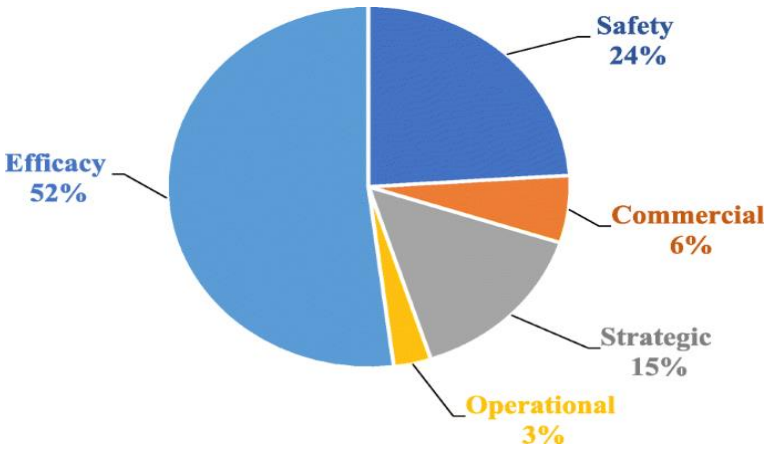
It is an established fact that majority of diseases have a molecular or genetic etiology [12, 13]. Some conditions including sickle cell disease, cystic fibrosis, muscular dystrophy, and Huntington disease are caused by single gene mutations [14]. Syndromic conditions such as diabetes and cardiovascular diseases have multifactorial causes including multiple gene mutations confounded by environmental and lifestyle factors [12]. In the concept of drug discovery, genes have therefore been classified as disease genes, disease-modifying genes, and druggable genes [15]. Disease genes are those whose mutations cause or predispose a person to the development of a given disease [16]. Disease-modifying genes encode functional proteins whose altered expression is directly linked to the etiology and progression of a given disease. Druggable genes encode proteins that possess recognition domains capable of interacting with drug molecules eliciting a pharmacological response [17].

In the current era of target-based drug discovery, it is imperative that the target is scrupulously identified and validated to establish its essentiality in the disease phenotype. This prevents

downstream attrition with available data indicating that a significant proportion (52%) of drug failure in clinical trials is due to poor efficacy. Figure 2 depicts the various causes of attrition [18, 19]. Classical cases of the drugs imatinib and trastuzumab exemplifies the value of careful target identification and validation in enhancing the success of the drug discovery process [20,21,22]. While the above were new molecules carefully designed with the knowledge of the underlying genetic mutation, existing drugs may find new applications through repositioning from their approved indications based on information obtained through genomics [23]. Genomics can be used to identify and validate druggable genes thus expanding the number of targets available for exploration in drug discovery [17, 24]. The use of genomics in target validation has expansively widened through advancement in antisense technology, small interfering RNA (siRNA) that mimic the natural RNA interference (RNAi) and transgenic animal models [25].

Exploitation of genomics is not restricted to target identification and validation. Rather, recent trends in pharma R&D show that genomics may be employed in the recruitment of study participants for clinical trials with the selection favoring those subjects more likely to benefit from the intervention being trialed. This ensures that the effect of the drug will be evident if the drug is indeed effective against the target disease and absent if ineffective.

The outcome so observed would therefore be attributable to the therapeutic intervention and shielded from other confounders. Genomics can also be used as a predictive tool to forecast potential toxicities emanating from a specific molecule [22]. Not surprising, the discipline of pharmacogenomics where drugs are adapted to meet individual profiles is fast gaining traction among researchers and medical practitioners, and has positively impacted the process of drug discovery and development [22].



The human genome was fully described in the year 2002, uncovering a vast treasure trove from which a wide array of novel drug targets could be discovered. Nonetheless, the scientific hype that was associated with the genome project has not been followed with solid benefits as less than 500 of the potential 10,000 targets have been utilized according to the repertoire of drugs registered by the United States Food and Drug Administration (US-FDA) [1, 26]. These targets are protein molecules including DNA, RNA, G protein-coupled receptors (GPCRs), enzymes, and ion channels. The GPCRs constitute the largest proportion of targets for currently registered molecules [27]. It is however expected that the genomic revolution will enhance the drug discovery process significantly given the intensive research currently being done in this field [28].

Proteomics which is a subset of genomics has been widely explored as an avenue of drug discovery [29]. Proteomics entails identification, characterization, and quantification of cellular proteins with the aim of establishing their role in the disease progression and the underlying potential for chemotherapeutic manipulation [25]. Proteomics has been applied widely in drug discovery projects for antineoplastics, neurological, cardiovascular, and rare diseases [30]. Technologies used in proteomics include gel electrophoresis for protein separation and characterization, mass spectrometry (MS) for identification, and yeast hybrid systems to study protein-protein interactions [31]. These approaches have the potential to identify novel drug targets and their corresponding genes.

Complementarity of phenotypic and target-based screening platforms

Two distinct screening approaches are routinely employed in the efficacy studies, namely phenotypic (whole-cell) screening and target-based (biochemical) screening. Phenotypic screening evaluates the effects of potential drugs on cultured cell lines (in vitro), isolated tissues/organs (ex-vivo), or in whole animals (in vivo) while target-based screening involves testing the molecules on purified target proteins in vitro [32]. In the first instance, phenotypic screens are primarily aimed at identifying molecules capable of eliciting the desired pharmacological effect without necessarily elucidating the underlying mechanism of action at the molecular level. They are therefore empirically driven as they focus on phenotypic endpoints. Phenotypic drug screening is information-rich, and the therapeutic relevance of the drug is established much earlier in the drug discovery process. The approach is more physiologically relevant as it is conducted in biological systems that simulate the real physiological environment where cognizance that pharmacological effects result from an interplay of many factors is well appreciated [33, 34]. It also provides a huge biological

space for serendipitous drug discoveries [32, 35]. On the contrary, target-based screening is hypothesis-driven, systematic, and rational. Of essence, it requires identification and isolation of a biochemical target whose modulation leads to a desired pharmacological effect. It employs advanced molecular technologies and biological methods that are facilitative of high throughput screening (HTS) platforms [36].

Whereas phenotypic screening predominated in the decades before 1980, it has largely been de-emphasized as advances in molecular biology, and genomics took root and favored the target-based screening [37]. The significant decline in the discovery of first-in-class molecules has in part been attributed to an increasing emphasis on the target-based drug discovery approach [34]. Analysis of data of the drugs registered by the US-FDA reveals that phenotypic drug discovery has yielded more first-in-class molecules than target-based screening [38]. These findings have been challenged by a study that established that 78 of 113 first-in-class molecules registered between years 1999 and 2013 were discovered using target-based screening approaches [39]. Target-based drug discovery has been the predominant approach of screening putative molecules in the last three decades [33, 42]. This has majorly been due to advances in cloning technologies that allow isolation of pure proteins that are then used to screen a large library of compounds using HTS. The high screening capacity afforded by this approach has cemented target-based platform as the default drug discovery approach as companies seek a competitive edge to deliver novel molecules to the market [36]. Target-based drug discovery begins with understanding the pathophysiological basis of the disease and subsequent identification of the errant biochemical pathway that leads to the disease phenotype. The specific protein that is aberrantly expressed is identified, isolated and its role in the disease phenotype validated by modulation using genomic or pharmacological approaches.

Target-based drug discovery, therefore, elucidates the specific mechanism through which potential drugs produce a pharmacological response. While it lags behind the phenotypic drug discovery approach in yielding first-in-class molecules, target-based drug discovery is unrivalled in producing the best-in-class follower molecules [38]. This is due in part to the rational, hypothesis and systematic approach employed leading to highly selective, potent molecules with better pharmacokinetic and toxicological profiles. Target based-drug discovery has the advantages of being simpler to undertake, enable faster development, and it enables elucidation of the underlying mechanism of action. It also enables the utilization of modern technological advances including computational modeling, molecular biology, combinatorial chemistry, proteomics, and genomics.

Conversely, since the approach is based on the modulation of isolated protein targets, the observed effect may have little physiological relevance as there is oversimplification of the physiological environment in which the drug molecules are evaluated [43].

Collaborative research

By its nature, the corporate pharmaceutical industry is highly competitive with each company aspiring to dominate the race to launch new blockbuster molecules. It is an established industry fact that early market entrants reap more than those who launch follower molecules. Pioneer companies are able to establish strong brand recognition as well as patient and physician loyalty before competition enter the market [55]. Further, early entrants have sufficient time to perfect their product and set the market price. At any given time, the pharma companies are working to discover and develop molecules addressing similar or very closely related drug targets. Given the astronomical funding channeled into pharmaceutical R&D, these duplicated research efforts collectively end up utilizing resources that could better be invested in the R&D of other disease areas with unmet medical needs. A number of collaborative arrangements have been proposed and utilized for greater success of the pharma R&D. These include precompetitive research, pharma-academia collaboration, and public-private partnerships (PPP) models [56].

The precompetitive research entails collaboration among pharmaceutical companies, biotechnology companies, and the academic drug discovery units that would otherwise compete but are brought together by a common desire to conduct fundamental research that is facilitative of subsequent drug discovery and innovation. In essence, precompetitive research establishes scientific viability of pursuing a given therapeutic pathway prior to initiation of full-throttle drug discovery and development campaign. Some of the areas in which precompetitive research may be practiced include target identification and validation, sharing of compound libraries, and biomarker and assay development. There are numerous benefits deriving from precompetitive collaboration including reduced costs of research as companies share their resources and expertise, greater efficiency as companies focus on their core competencies thus furthering their excellence, and cross-fertilization of scientific ideas [57]. Precompetitive collaborations are modeled as virtual institutions with scheduled video conferences to monitor and evaluate the progress made. Once the objectives set upon are attained, companies can then venture into separate drug discovery projects [58]. Renown precompetitive collaborations include the Biomarkers Consortium, Innovative Medicine Initiative

and TranSMART [59]. TransMART is an inter-organizational collaboration including government agencies, academia, and patient advocacy groups that serves as an open data warehouse arising from clinical trials and basic research [60, 61]. In recognition of the potential gains that could accrue from precompetitive collaborations, the US-FDA developed guidelines for registration of drugs discovered through collaborative strategies in 2011 [62].

Under-served therapeutic fields

Strategic considerations are vital before a company commits to a drug discovery project. Among the key considerations is the economic viability of a potential drug molecule upon market entry. For sustainable pharma R&D, any drug development candidate must have an acceptable return on investment to ensure the discovery company remains a viable going concern and is able to fund other drugs in the research pipeline. As such majority of the pharmaceutical R&D efforts are inclined to the therapeutic areas with vast economic potential such as oncology, immunotherapy, endocrinology, neurology, and cardiovascular fields where the probability of recouping the huge capital investment is more certain [41]. Therapeutic areas that offer negligible financial benefits such NTDs and rare diseases do not attract much attention and therefore the opportunities for novel discoveries largely remain unexplored [70]. Rare diseases are genetic disorders that afflict a small patient population and thus offer little economic promise. The NTDs, on the other hand, are vector-borne diseases that afflict billions of people in resource-poor countries. However, these populations have low purchasing power and as such, the pharma companies may not recoup their investments let alone enjoy profitability [71].

Pharmaceutical modeling and artificial intelligence

Modeling entails the use of in silico simulations to predict diverse attributes of a drug molecule including pharmacokinetics and pharmacodynamics profiles [80]. Advances in computing power have enabled development of software that allows simulation of the drug-receptor binding processes, a subset of computer-aided drug design (CADD) also referred to as virtual screening, with tremendous benefits to drug discovery efficiency. First, CADD facilitates generation of focused screens that are then validated in vitro. Second, the CADD is well positioned to guide the lead optimization process thus providing valuable information to the medicinal chemistry team aspiring to enhance the lead molecules receptor affinity or optimize drug metabolism and pharmacokinetics (DMPK) properties including absorption, distribution, metabolism, excretion, and the potential for

toxicity (ADMET). Third, the CADD facilitates rational drug design either by "growing" starting molecules one functional group at a time (de novo drug design) on the target site or by piecing together fragments into novel molecules (fragment-based drug design) [81]. Two screening approaches, namely ligand-based virtual screening and target-based virtual screening, have been used in CADD to filter out the compounds that are unlikely to be successful in the development pipeline due to poor physicochemical properties and/or intolerable toxicological profile while identifying those likely to have the activity of interest.

In ligand-based virtual screening, structural features of known compounds are used to construct computer models that are used to predict the properties of other compounds not included in the training data set. The data sets are then used to generate quantitative-structure activity relationship (QSAR) models correlating structural features and the physicochemical properties of a homologous series to the observed biological activity. The chemical structure of known compounds is reduced to a set of molecular descriptors that are used to generate a mathematical model that is used to predict the properties of the test compounds. Molecular descriptors with the highest activity are chosen for the model [82]. Target-based virtual screening entails computer models that test the docking properties of test compounds against the three-dimensional structure of the target (X-ray crystal structure or homology model) [83,84,85]. Each of the test compounds is optimally positioned on the binding site and assigned a score based on the binding affinity. Top scoring compounds are synthesized and tested in vitro [86]. Application of these models can enhance the efficiency of drug discovery projects by providing focused screens that can have better chances of succeeding downstream. Problematic molecules are also identified earlier in the drug discovery process thus avoiding expensive late-stage failures. Integration of ligand-based and target-based virtual screening yields better results [32, 87].

Conclusion

The ever-increasing costs of drug discovery projects have not translated into increased efficiency in delivering new medicines. On the contrary, fewer drugs are transiting through the drug development pipeline than ever before. The observed productivity decline is majorly attributable to the overreliance of the industry on high technology platforms, stringent drug registration and approval requirements for new medicines, and the exhaustion of the obvious and easy-to-reach drug targets necessitating exploration of more complex biological systems.

Scientific advancements allow the application of advanced molecular techniques that include genomics and lately proteomics in identification and validation of drug targets. Carefully executed target identification and validation will reduce the attrition rates attributable to poor efficacy that currently accounts for more than 50% of drug failures. The complementarity of phenotypic and target-based drug discovery approaches would enable discovery of first-in-class molecules while also delivering safer, more efficacious and potent best-in-class follower molecules.

Collaborative strategies, such as precompetitive research and public-private partnerships, have positively impacted efficiency in drug discovery. Expansion of research activities into the underserved therapeutic areas covering rare and neglected diseases would offer a safeguard for companies whose blockbuster drugs are teetering on the patent cliff. Advances in computing technologies will also facilitate selection of focused screens with better success rates downstream. Pharmaceutical modeling and AI are expected to continue contributing significantly to improved efficiency in drug discovery and development in the years to come. Carefully executed outsourcing strategies allow companies to focus on their core competencies while delegating other development activities to expertise offered by the CROs, a strategy that accelerates the discovery process while reducing overhead costs.

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