CHAPTER

DRUG DISCOVERY AND DEVELOPMENT: AN OVERVIEW 2

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2.1 INTRODUCTION

Drug discovery is a process which is intended to identify a small synthetic molecule or a large biomolecule for comprehensive evaluation as a potential drug candidate. Broadly, the modern drug discovery process includes identification of disease to be treated and its unmet medical need, selection of a druggable molecular target and its validation, in vitro assay development followed by high throughput screening of compound libraries against the target to identify hits, and hit optimization to generate lead compounds that exhibit adequate potency and selectivity towards the biological target in vitro and which demonstrate efficacy in animal models of disease. Subsequently, the lead compounds are further optimized to improve their efficacy and pharmacokinetics before they advance towards drug development (Fig. 2.1). Drug development process can be segregated into preclinical and clinical development stages (Fig. 2.2). In preclinical development, toxicological and safety pharmacology studies of the candidate are conducted in order to establish the maximum safe concentrations in animals and determine the adverse effect potential of the drug-in-development. Additionally, studies are conducted to finalize cost-effective processes required for manufacturing the candidate drug as well as deciding on its best formulation. If the candidate exhibits sufficient efficacy and safety in preclinical evaluation, permission is sought from drug regulatory agencies to initiate its clinical development wherein the safety and efficacy of the drug candidate is assessed in pilot and pivotal studies.

The discovery and development of innovative drugs is time and cost intensive and currently approximately twelve years and an average of $1.8 billion is required to launch a new drug. Over the years, there is a decreasing trend in the number of innovative drugs obtaining marketing approval. This is a consequence of heightened scrutiny of the safety and efficacy of new drugs by regulatory agencies, which leads to increased costs and prolonged development times. Further, the top management of pharmaceutical industry wants to avert the risks associated with drug discovery and development. Moreover, pressure on national health services due to costs associated with pharmaceuticals has an adverse impact on their pricing. Additionally, patent expirations and their generic substitutions have reduced the profits and subsequent growth of the pharmaceutical industry, resulting in reduced investment in innovative research. A new concern is adverse environmental impact of pharmaceuticals and there are clear directives from governmental agencies to ensure steps to reduce this impact [1]. A direct consequence of the dismal drop in productivity is increased

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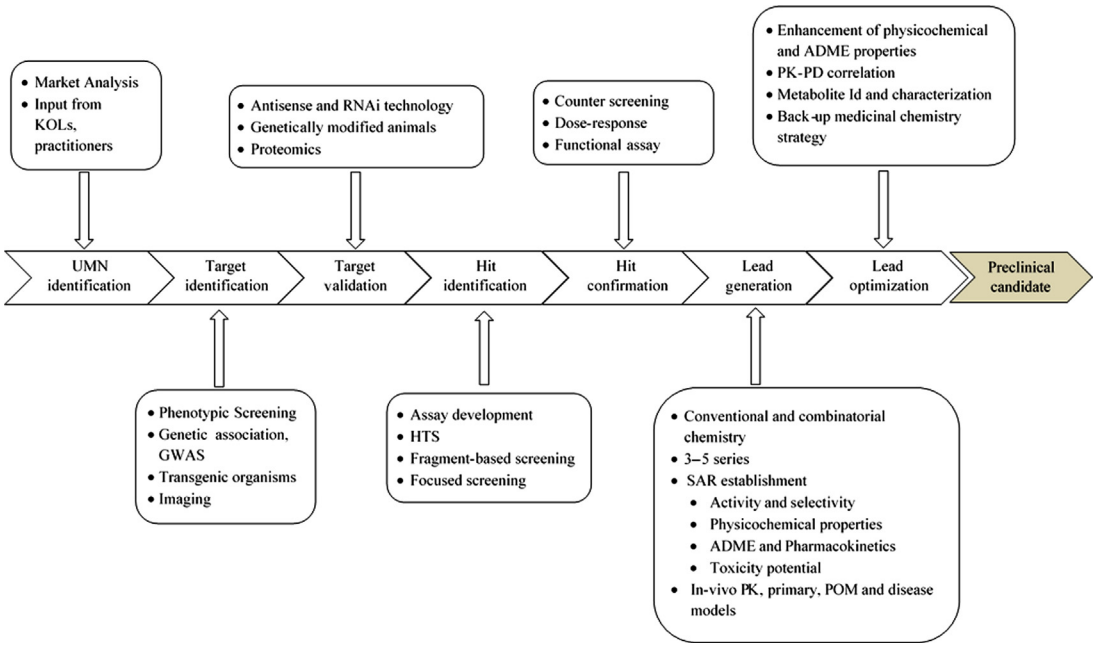

FIGURE 2.1

Overview of drug-discovery process. *UMN*, unmet medical needs; *KOL*, key opinion leader; *SAR*, structure activity relationship; *GWAS*, genome wide association studies; *HTS*, high throughput screening; *POM*, proof of mechanism; *PK*, pharmacokinetics; *PD*, pharmacodynamics.

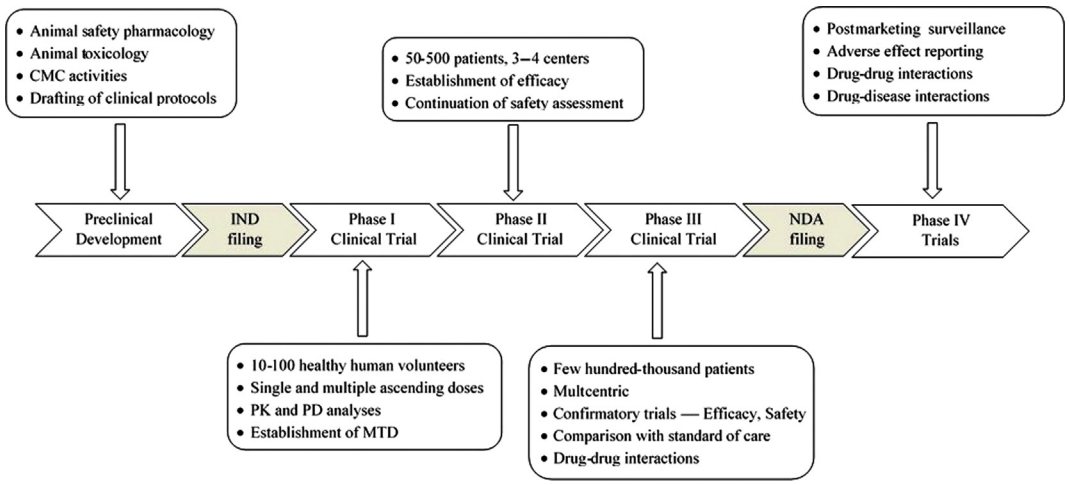

FIGURE 2.2

Overview of drug development process. *CMC*, chemistry, manufacturing and controls; *MTD*, maximum tolerated dose; *IND*, investigated new drug application; *NDA*, new drug application.

mergers and acquisitions seen in pharmaceutical industry, with the primary objective of reducing R&D costs and creating synergies. However, investments in innovative research post-mergers and acquisitions and pipeline advancements have actually decreased and hence industry consolidation to increase productivity is questionable [2].

In spite of the fall in R&D productivity due to the above mentioned concerns, there is still a high unmet need in the therapeutic areas of cancer, Alzheimer's disease, and diabetes, and there is a global emergence of multidrug resistant bacterial infections for which innovative drugs are urgently required.

2.2 IDENTIFICATION OF UNMET MEDICAL NEED

The trigger to initiate a drug discovery program is a medical condition whose treatment is not satisfactorily addressed by currently available treatment modalities. This is referred to as an unmet medical need for that condition. To elaborate, new drugs are needed either to treat a disease for which no other treatment exists or which offer additional advantages over existing treatments like superior therapeutic efficacy, reduced adverse effects, improved compliance, fewer drug-drug interactions, and consequently an overall improvement in the quality of life of a patient. Approaches to identify the unmet medical need include market analysis, inputs from key opinion leaders in a therapeutic area, feedback from medical practitioners and scientific conferences. Additionally, a thorough understanding of disease etiology, epidemiology, available therapeutic options and their shortcomings drive a prudent gap analysis and thereby facilitate shortlisting of medical needs in particular disease condition.

2.3 TARGET IDENTIFICATION

Biologically active compounds, whether they be a small synthetic molecule or a large molecular weight antibody, elicit their activity and thereby a measurable clinical effect by interacting with a naturally existing molecular structure, which in the context of drug discovery is referred to as a "target." These include enzymes, receptors, metabolites, substrates, ion channels, transport proteins, DNA, RNA, and ribosomes [3]. These targets can broadly be classified into established and novel targets. The targets which have been scientifically proven to have well-defined physiological and pathophysiological roles fall in the former category, whereas newly discovered ones whose role is turning out to be clearer with advancing research constitute the latter class. The various approaches to target identification are briefly discussed below.

In the phenotypic screening approach, compounds or antibodies are evaluated in cell-based assays or animal models of disease with an aim to identify compounds which elicit an anticipated change in the phenotype. This may include change in expression of a single or multiple proteins in vitro or obtaining desired pharmacological response in vivo. Subsequent to the identification of an active compound, its molecular target is then determined by genetic approaches like expression cloning techniques, in silico approaches, or chemical proteomic based approaches like affinity chromatography, activity based protein profiling, and label free techniques [4]. To exemplify, in an

elegant study conducted by Sandercock et al., [5], single chain variable fragment (scFv) antibodies and designed ankyrin repeat proteins (DARPins) against primary non-small cell lung carcinoma cells were isolated and evaluated for pro-apoptotic and antiproliferative activity against primary cells. The phenotypic changes were detected in an ultra-high content screen by using multiple parametric profiling and subsequently CUB domain containing protein 1 (CDCP1) was identified as a target by employing a cell-surface membrane protein array.

Another process employed for target identification is genetic association study, wherein genetic variants—like single nucleotide polymorphisms (SNPs)—associated with risk for a disease or its progression, are identified. For example, distinct vascular endothelial growth factor (VEGF) polymorphisms lead to predisposition for psoriasis and hence modulation of VEGF signaling pathway might be a potential therapeutic option for the disease [6]. Further, genome wide association studies (GWAS) that explore the entire human genome for a large number of SNPs at a time, with an aim of identifying those variants that occur in most patients with a complex disease, have also aided in target selection as well as repositioning of existing drugs [7]. For example, denosumab, which is indicated for osteoporosis, targets tumor necrosis factor super family member 11 (TNFS11). However, GWAS suggest that the gene for this target is also associated with Crohn's disease and hence denosumab may have potential therapeutic utility in this disorder as well [8]. Transgenic organisms are also employed in target identification. For example, through bacterial artificial chromosome (BAC) transgenics in mice, the putative genomic region linked to a disease phenotype can be identified and further can be narrowed down to the target gene of interest [9]. Molecular and functional imaging techniques are also valuable tools for target identification [10].

2.4 TARGET VALIDATION

Subsequent to identification, a potential drug target needs to undergo the process of validation wherein its function in a disease state is ascertained. There are multiple approaches towards validation and some of them will be discussed here.

Use of antisense technology is a popular route wherein short oligonucleotides (single stranded nucleic acids), complimentary to a specific region of a messenger RNA of interest, are designed. The interaction of the oligonucleotides with the target mRNA results in disruption of translation and subsequently impedes the synthesis of the protein. To exemplify, knockdown of tetrodotoxin-resistant sodium channel $Na_v1.8$ by antisense oligonucleotides, obliterated intrathecal *N*-Methyl-D-Aspartate-induced mechanical hypernociception in rats, thereby highlighting the importance of these ion-channels in pain pathophysiology [11].

An alternative approach is RNA interference (RNAi) technology, wherein silencing of the target gene in a cell or an organism is triggered by introduction of a double stranded RNA (dsRNA) specific to the gene. The long dsRNAs are cleaved by the RNase, Dicer, into small interfering RNAs (siRNAs), which are double stranded fragments of 21−25 nucleotides with some unpaired base pairs at each end. Subsequently, the siRNAs are unwound into two single strands, referred to as a guide and a passenger strand, respectively. The guide strand is incorporated into the RNA interference specificity complex (RISC) and it locates the mRNA possessing the complimentary sequence, resulting in cleavage of the target mRNA and shutting down of the translation machinery. This

approach of using long dsRNAs is marred by variability in response, overall decrease in mRNA levels, and expensive design. Alternatively, these issues can be overcome by design and subsequently direct introduction of 21−25 nucleotide long siRNAs into the cellular machinery. The potential utility of the above modality in target validation is exemplified by an experiment conducted by [12], wherein mice injected with siRNA against the chemokine CCR2 and subjected to ischemia-reperfusion, demonstrated lower infarct size and marked decrease in cardiac inflammatory monocytes as compared to control siRNA administered mice, thus demonstrating the role of CCR2 in inflammatory cell trafficking in cardiac tissue.

Employing genetically modified animals for target validation is an appealing methodology as it permits the scrutiny of the phenotypic consequences of gene manipulation. Development of knock-outs, knock-ins, conditional knock-outs, and transgenic animals are instances of genetically modified animals. An animal lacking a particular gene from the embryonic stage is one approach to studying the in vivo functions of diverse genes. For example, contraction to carbamylcholine was virtually abolished in the urinary bladder from muscarinic M_3-receptor knock-out mice, suggesting that contraction was predominantly due to M_3 receptor activation [13]. In gene knock-in animals, the desired gene is inserted into a specific locus in the target genome and can hence be said to be a gain of function mutation. To exemplify, knock-in mice with deficits in the AMPA receptor GluR1 Serine 831 and Serine 845 phosphorylation had a higher threshold and longer latencies to pentylenetetrazole induced seizures in postnatal day 9 as compared to wild type mice thereby supporting the validation of this potential therapeutic target for neonatal seizures [14].

In a conditional knock-out approach the gene of interest is deactivated in the target tissue at a specific time point thereby limiting the risk of embryonic lethality and developmental abnormalities which are often experienced with conventional knock-out models. The utility of this approach in target validation can be exemplified by a study conducted by [15] wherein they show that mice in which GPR88 receptor located on adenosine $A_{2A}R$ neurons were conditionally knocked-out, demonstrated decreased anxiety-like behaviors in light/dark and elevated plus maze tests.

Transgenic animals are also an attractive validation tool wherein a foreign gene is intentionally inserted in their genome. For example, transgenic LXR α mice demonstrated improved myocardial glucose tolerance and reduced cardiac hypertrophy in a mouse model of obesity-induced type 2 diabetes thus supporting use of therapies targeting LXR α for cardiovascular diseases [16].

A limitation of the genetic approach to target validation is that genes generate various isoforms of the protein which may have slightly different functions, and variations in proteins can also be a consequence of post-translational modifications. Hence, an improved and emerging approach to target validation is the proteomics approach which aims on the modulation of the activity of the target protein itself [17].

2.5 HIT IDENTIFICATION AND DEVELOPMENT OF ASSAYS

Following validation of a therapeutic target the next step is identification of ‘hits’, which in a broad sense may be defined as compounds that elicit the desired activity in a screening assay. For hit identification there exist diverse screening methods of which some will be briefly described. In a high throughput screening (HTS) method, libraries of, in some cases, up to a million drug-like

compounds may be directly and quickly evaluated against a protein target in a biochemical assay (wherein requirement for a protein is less) or a cell-based assay, if the target has proven to modulate the cellular activity. This involves complex automation like the use of robotic liquid handler systems. In this methodology, the researchers do not have prior information of the chemotype required for demonstration of activity against the target and as an outcome one or few compounds may be identified with the desired activity in the high affinity range (IC_{50} in μM). Some demerits of HTS include poor coverage of chemical space and difficulty in optimization due to complex nature of hits [18]. Subsequent to identification of hits and subject to accessibility of the three-dimensional structure of the protein, the compound(s) may be co-crystallized with the protein and through X-ray crystallography the structure of the protein-ligand complex is acquired. This aids in determining the structure of the binding site on the protein, thereby providing the information for hit optimization, and thus forms the foundation for structure based drug design.

Another method which is developing popularity is the fragment-based screening approach wherein libraries of small molecule fragments are evaluated at a high concentration and the hits are defined as compounds which although weak in activity show efficient binding. These fragments can be then be used as building blocks for the synthesis of potent and drug-like compounds.

In the focused screening strategy, limited sets of compounds that have demonstrated activity against a specific class of targets (e.g., GPCRs) or structurally similar compounds are evaluated in the assay. This approach also extends to virtual screening, wherein a virtual library of existing compounds may be docked with the three-dimensional protein structures and their activity against the target might be predicted computationally.

The principles of phenotypic screening and its applications in target identification have been previously discussed. The time-honored phenotypic route has been additionally proven to be effective in the discovery of first-in-class drugs. The alternative approach, which is termed as target based screening, involves assessment of the activity of a large number of compounds against a single protein target. This route has been successful in the generation of follow-up drugs, but its main disadvantage with respect to discovery of first-in-class molecules is cross reactivity with several other targets, which cannot be captured in the single protein assay setup [4]. Some examples of drugs discovered through phenotypic screening are: aripiprazole—a conformational/partial receptor agonist; azacitidine—an irreversible enzyme inhibitor; cinacalcet—allosteric activator of receptor; ezetimibe—affects transporter activity; and miglustat—an enzyme inhibitor demonstrating reversible inhibition. On the other hand, drugs discovered through target based screening include: eltrombopag—a non-competitive receptor agonist; imatinib—an enzyme inhibitor that works by stabilizing inactive conformation; mifepristone—a conformational receptor antagonist; orlistat—an irreversible enzyme inhibitor; and raltegravir—an enzyme modulator acting by trapping the conformational state [19].

For most of the hit identification strategies it is crucial to develop biological assays in which compounds are evaluated for their activity. Biological assays may be cell-free or biochemical assays in which human or other mammalian recombinant proteins are employed for evaluation of compounds either for their affinity as in the case of receptors or inhibitory activity for enzymes. Cell-based assays on the other hand are functional assays with a specific read-out, for example intracellular calcium concentration. Factors to be considered for a selection of an assay format include relevance of the assay, its reproducibility, assay quality, cost assessment, effect of compound or its solvent on the assay, and the screening concentrations [20].

2.6 CONFIRMATION OF HITS

In this phase the identified hits are subjected to confirmatory evaluation using the same assay conditions which were employed during hit identification. Further, it is imperative to ascertain that the activity is linked to the anticipated mechanism and is not due to artifacts. Subsequently, frequent or promiscuous hitters are eliminated from further consideration. A procedure of detecting false positives is to employ a counter-screening assay in which hits are evaluated for their activity against an alternative member of the target family under identical assay conditions and if the hit demonstrates similar activity then it is most likely a false positive. Additionally, precipitation of the small molecule as well as aggregate formation can also lead to false positive results and such a counter-screen aids in their exclusion from further attention [21]. Consideration must also be given to identifying compounds that may produce activity based on detrimental mechanisms, as these may lead to toxicity. Establishing dose-response relationships is also essential as an all-or-none response may point to non-specific effects or interaction with any other constituent of the assay condition. Additionally, generation of reliable dose-response curves allows rank ordering of hits through the estimation of half maximal inhibitory concentration (IC_{50}) in case of inhibitors/antagonists and half maximal effective concentration (EC_{50}) for activators/agonists. Experiments examining the nature of binding of the actives at this stage are also advantageous as they filter out compounds showing non-competitive interaction with the target and which will not be the preferred candidates for evaluation in a clinical setting. Finally, the hits may be screened in a secondary cell-based or a functional assay in which the target has been proven to play a role in order to ascertain their efficacy.

During hit-confirmation, medicinal chemists utilize the biological data to rank as well as cluster the hits into groups and gain initial insight into structure-activity relationships (SAR) between members of a group. Additionally, feasibility of chemical synthesis is also scrutinized by the medicinal chemists.

The potency of a hit identified against a target is usually in the range of 1 μM to 5 μM and in the next drug discovery phase chemists aim to enhance its potency and many other features, which will be explained in the following section (Fig. 2.1).

2.7 LEAD GENERATION

Lead generation, also referred to as hit to lead phase, involves optimization of the identified hits from a diverse series to generate lead compounds. Three to five chemical series are typically chosen for lead generation and analogous compounds are evaluated to establish a quantitative SAR towards activity, target selectivity, physicochemical properties, ADME properties, pharmacokinetics, and toxicity potential.

In this stage, compounds synthesis is initiated by medicinal chemists by using various approaches like conventional organic chemistry and combinatorial chemistry. Through the combinatorial chemistry approach large numbers of single compounds or mixtures of compounds can be synthesized in parallel and can be used for the synthesis of both small molecules and peptides. Combinatorial chemistry may be defined as the systematic and repetitive, covalent

connection of a set of different building blocks of various structures to one another to yield a large array of diverse molecular entities [22]. The advantage of combinatorial chemistry over the classical approach is faster synthesis of, in some cases, up to a million compounds simultaneously, and hence it aids in rapid as well as efficient discovery of lead compounds. In case of the synthesis of a concoction of compounds, the entire mixture may be subjected to evaluation of its activity followed by identification of its active component(s). If on the other hand no actives are found, then no further attention is given to the mixture. A drawback for a mixture of compounds is interference of one compound with another, and it is prone to generation of false-positive hits.

Screening flow for lead identification comprises of in vitro evaluation in primary/cell-free assays as well as specificity of the compounds for the target. Further, the activity of compounds is also evaluated in known animal orthologs of the target as the compounds have to be evaluated for their efficacy in animal models. Subsequently, data for active compounds is also generated in in vitro functional or cell based assays.

In addition, physicochemical properties of representative compounds from the series being explored are also studied to confirm drug-likeness of the compounds. As the most preferred route for administration of the drug is oral, the new chemical entity in development should observe the Lipinski rule of 5 which asserts that a compound is more likely to be membrane permeable and absorbed by the body if it matches the following criteria [23]:

- Its molecular mass is less than 500 daltons
- Its logP, which is a measure of lipophilicity, is less than 5
- The number of hydrogen bond donors is less than 5
- The number of hydrogen bond acceptors is less than 10

Solubility assessments are additionally conducted as it has a bearing on both in vitro and in vivo assays as well as its absorption from the intestine, and the objective of the medicinal chemists is to obtain compounds having a solubility of $>60\ \mu g/mL$ [24].

Further, the in vitro ADME properties of compounds are also profiled. These include permeability assessment in colon carcinoma (Caco-2) cell line as a model for intestinal absorption [25], metabolic stability evaluation using human liver microsomes to determine the intrinsic clearance [26], cytochrome P450 inhibition and induction to assess whether the compound will have the potential to influence the metabolism of concomitantly administered drugs [27] and plasma protein binding assay which has a bearing on drug distribution and overall pharmacological action [28]).

It is also prudent to assess the toxic potential of compounds in the early stage of drug discovery, and several in vitro assays employing human cell lines have been developed to address this evaluation. These include cytotoxicity assays to investigate the effect of compounds on cell viability [29]; hERG inhibition assay using hERG overexpressing cell lines to predict the QT interval prolongation liability of the compounds under investigation [30]; hepatoxicity assay using a variety of systems like hepatic cell lines, isolated liver cells in suspensions, liver slices, and subcellular fractions [31]; in vitro micronucleus assay [32] to assess the potential for genotoxicities like clastogenic activity (structural aberrations in chromosomes); and aneugenic activity (numerical chromosome aberrations).

Potent and selective compounds having desirable physicochemical and ADME properties are also profiled for their pharmacokinetics in the same animal species in which the efficacy of the

compounds have to be evaluated. Compounds having appropriate pharmacokinetics are then evaluated in primary animal models, which may also include proof of mechanism models that demonstrate target engagement. Finally, compounds are screened in animal models of human disease for their efficacy.

2.8 LEAD OPTIMIZATION

The goal of lead optimization is to generate preclinical development candidates by improving the shortcomings of the lead structure by chemical modifications. Generally, the aim is to enhance the physicochemical and ADME properties and minimize the toxicity liabilities so that a potentially safe compound with favorable pharmacokinetics is identified.

It is important to demonstrate a direct correlation between concentrations of the compound in plasma with its pharmacodynamic effect, and such data might be later utilized to predict dosing regimen of the compound. Additionally, it also beneficial to establish dose-linear exposure, as the compounds which do not exhibit such behavior have limited clinical utility, particularly if they have a narrow therapeutic window. Identification and characterization of the metabolites of the compound is also conducted during this stage as metabolites may influence the compound efficacy, may themselves be active, may elicit toxicities, and additionally active metabolites may be considered as new exploratory lead structures for the medicinal chemists.

Medicinal chemistry does not conclude once a preclinical candidate has been identified, as the chemists initiate effort on a back-up strategy with an aim to identify compounds that can substitute for any failures in preclinical and clinical development.

2.9 PRECLINICAL DRUG DEVELOPMENT

Once a preclinical drug candidate is selected, the drug development process begins. The drug is progressed through various studies designed to support its approval by the regulatory bodies to move the candidate into clinical (human) study by submission of an Investigational New Drug (IND) application. The preclinical development program consists of various activities, including safety pharmacology and toxicology studies in animals and other activities related to chemistry, manufacturing, and control (CMC) such as formulation development, stability studies and quality control measures etc. and detailed proposed clinical protocols for initiating clinical studies. For details on preclinical development and safety pharmacology, toxicology, please refer to Chapter 4, on Preclinical Drug Development (Fig. 2.2).

2.10 CRITERIA TO SELECT A CLINICAL CANDIDATE

A compound should demonstrate the following properties for selection as a clinical candidate [33]:

1. *Chemical properties*: It should be a stable molecule whose synthesis is simple and can be scaled up with ease.

2. *Physicochemical properties*: It should observe Lipinski rule of 5 and should have acceptable solubility.
3. *Pharmacological properties*: It should bind with the target site with high affinity, should demonstrate selectivity for its molecular target and should elicit potent functional effect in vitro. Efficacy of the compound should be demonstrable in animal model of human disease.
4. *Pharmacokinetic properties*: It should possess acceptable bioavailability, adequate half-life and proper distribution in animals. Metabolic pathways of the compound should be well characterized and activities of metabolites should be evaluated.
5. *Safety and toxicity potential*: It should be devoid of cardiac toxicity (hERG binding), genotoxicity, and hepatotoxicity, and should demonstrate an acceptable profile for induction and inhibition of cytochrome P450 enzymes. Ultimately it should be devoid of any serious animal toxicity.

2.11 CLINICAL DRUG DEVELOPMENT

If the IND is approved, clinical drug development begins. For details, please refer to Chapter 5, on Target Product Profile and Clinical Development. The general goals of various phases of clinical trials are similar even though the designs of these trials can be substantially different. In general, a phase I trial is conducted to assess safety and tolerability of a drug and is usually conducted on 10−100 healthy volunteers. Both pharmacokinetic (ADME) and pharmacodynamic aspects are monitored. The maximum tolerated dose (MTD) is determined. The trial is generally open-label (nonblinded). Phase II trial is the first study that investigates clinical effectiveness of the drug and hence this is carried out in patients. In this trial, about 50−500 patients receive the investigational new drug mainly to assess efficacy of the drug in patients. However, the trial can have multiple objectives like studying dose-response relationship and determining dosing regimen (optimum dose and frequency of administration, etc.). The safety assessment continues as in Phase I. The trial is generally randomized and controlled and may be single or double blind trial. The majority of clinical candidates fail in this phase due to lack of efficacy or safety issues. Phase III trials confirms the efficacy of investigational drug in a larger population, usually a few hundred to a few thousand participants (patients). The trial is multicentric (conducted at multiple sites) and compares the investigational drug with the best existing treatment or standard of care in that particular disease. The safety is also assessed in a larger pool so that less common adverse events may be detected. They are typically randomized, controlled, double-blind trials with multiple study arms, and are the most expensive and complex trials. If positive results are obtained, all data till date is compiled into a dossier and a New Drug Application (NDA) is filed for regulatory approval to license the drug. Once the drug is marketed, post-marketing surveillance or Phase IV trials begin as additional follow-up studies to detect rare or long-term adverse effects across a much larger population or effects in certain special population, drug-drug or drug-disease interactions, etc. mainly to test the drug in a real world setting. Phase IV studies have huge implications, including altering the labeling of the drug, contraindications, interactions, and even withdrawal of a marketed drug. The Phase IV studies are described in detail in Section VII Pharmacovigilance (see Chapters 26−31).

2.12 OTHER APPROACHES IN DRUG DISCOVERY AND DEVELOPMENT

One of the reasons for fall in the number of innovative drugs is one-drug-one target paradigm and due to the involvement of multiple targets in complex diseases it is prudent to modulate them simultaneously. This can be achieved with either different or a single agents, with the latter being challenging from a medicinal chemistry perspective. However, discovery of new drugs for Alzheimer's disease has shown some promise with this approach [34].

Another alternative approach is repositioning existing drugs for new indications (repurposing). An example in this case is of thalidomide, which was originally approved as a sedative, was later approved for leprosy, and now has been licensed for treatment of multiple myeloma. An advantage of this approach is the bypassing of preclinical safety as well as Phase 1 trials, which saves the industry a lot of time and money [35].

Allosteric modulation of drug targets is another novel approach towards drug discovery, wherein drugs bind at binding sites of the biological target—which are distinct from the active sites. A benefit with this approach is that while active sites might be common in several proteins, the allosteric sites might be unique, which allows for selective targeting and consequently either fewer or target-specific adverse effects. For example, a positive allosteric modulator of M_1 muscarinic receptor, benzylquinolone carboxylic acid (BQCA), has shown efficacy in animal models of schizophrenia [36].

Natural products have been the most valuable sources for small molecules for the treatment of diseases and as leads for drug discovery, but chemical modifications are required to improve their physicochemical properties and to generate derivatives for SAR, which is often challenging. However, new approaches are under development to overcome the bottlenecks to enable a full exploitation of their potential in generating innovative drugs [37].

Pharmaceutical industries are also venturing into discovery and development of biologics or biologically derived medications which have the potential to generate blockbusters in the future. These include monoclonal antibodies, polypeptides, hormones, growth factors, interferons, and interleukins as well as vaccines, and require recombinant DNA process for their production. They work by targeting either a genotype or a protein target. However, they are quite expensive, complex to manufacture, and being mainly proteins they have the potential for immunogenicity. Generally, the target patients are those on whom the conventional therapies do not work or for whom no therapeutic options exist [38].

Crowd sourcing which involves collaboration between pharmaceutical industry and academia is being actively pursued to promote innovation in early drug discovery research typically through the use of internet with the optimism to increase R&D productivity [39].

Network pharmacology is an emerging paradigm in drug discovery, which aims at revealing synergistic interactions between individual drugs administered in combination and thereby determining the group of proteins which are most significant in disease pathophysiology. Subsequently, the goal is to identify molecules which target those proteins [40].

As to which of these strategies would yield the desired results remains to be seen. Science and the long-term approach would be the foundation and the way forward to support innovation. While following these strategies, it is important to get the right attrition at proper times and look for low risk and high pay of drugs.

With respect to clinical drug development, microdosing is an approach which has played a useful role in increasing R&D productivity. Here, a subpharmacologically active dose is administered to humans, and exploratory pharmacokinetics of the parent or its metabolite are studied. This phase is also referred to as Phase 0 and regulatory agencies grant approval for its conduct without a full preclinical safety package. The compounds showing poor pharmacokinetics are dropped from further development [41].

Clinical development is the most expensive stage in drug development and it has been suggested that we should move away from the conventional approach based on different phases towards an integrative view in which one uses adaptive design tools to increase flexibility and maximize use of accumulated knowledge, which could result in achieving the desired goal [42].

2.13 CONCLUSION

Pharmaceutical industry is currently under immense pressure due to rising costs, pricing, and risks associated with drug discovery and development. However, due to high unmet medical needs, the disease treatment will continue to be determined by innovation generated by the industry in collaboration with academic institutions and other modes of public-private partnerships. Intellectual property protection, however, is important in supporting pharmaceutical R&D. New developments in science and technology and other innovative and emerging approaches to improve R&D productivity need to be adopted with a long-term approach in order to be truly supportive of novel drug research.

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