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Review Article

CURRENT TRENDS IN DRUG DISCOVERY: TARGET IDENTIFICATION TO CLINICAL DEVELOPMENT OF THE DRUG

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ABSTRACT
The practice of the drug discovery process has been revolutionized with the involvement of some newer techniques. Target based drug design is more advantageous, time consuming and effective. With the use of High Throughput Screening (HTS) technique a large number of compounds screened for their biological activity with the discovered)) target, which are synthesized by combinatorial chemistry, these are called hits. Quantitative Structure Activity Relationships (QSAR) constitutes immense importance in discovering new drug candidate called analogues which shows high affinity with the target. Various advanced techniques and Modern research disciplines such as genomics, proteomics, metabolomics, chemogenomics, and others improve the quality of the drug discovery process. The main objective of this article is to highlight the steps and trends followed in drug discovery process and also to understand the mechanism for searching the ailment of disease.
Key words: Drug discovery, QSAR, Target, receptor

INTRODUCTION

The drug discovery process was beginning in nineteenth century; by John Langley in 1905 when he proposed the theory of receptive substances. The first rational development of synthetic drugs was carried out by Paul Ehrlich (father of modern chemotherapy) and Sacachiro Hata who produced arsphenamine (Salvarsan) in 1910 by structure activity relationship from atoxyl used in sleeping sickness (trypanosomiasis) and syphilis[1]. Ehrlich was awarded by Nobel Prize in 1908. In 1960 Hansch & Fujita introduced the concept of QSAR (quantitative structure–activity relationship). After that in 1970 the process is advance due to the involvement of molecular modeling and combinatorial chemistry.

Drug discovery and development can broadly follows two different approaches: structure based drug discovery and target-based discovery[2]. In structure based drug discovery a compound is identified by one of several methods and its biological profile is explored. In structure based if the compound displays desirable pharmacological activity, it is refined and developed further where as in target based strategy putative drug target is identified first. The potential target could be a receptor thought to be involved in a disease process or a critical enzyme, or another biologically, important molecule in the disease pathway. The two approaches are not mutually exclusive, and drug discovery projects can employ a two pronged approach. The genomics revolution has been the main driver of the target-based strategy over the last decade. Target validation requires the confirmation that whether the particular target is involved in the disease or not.

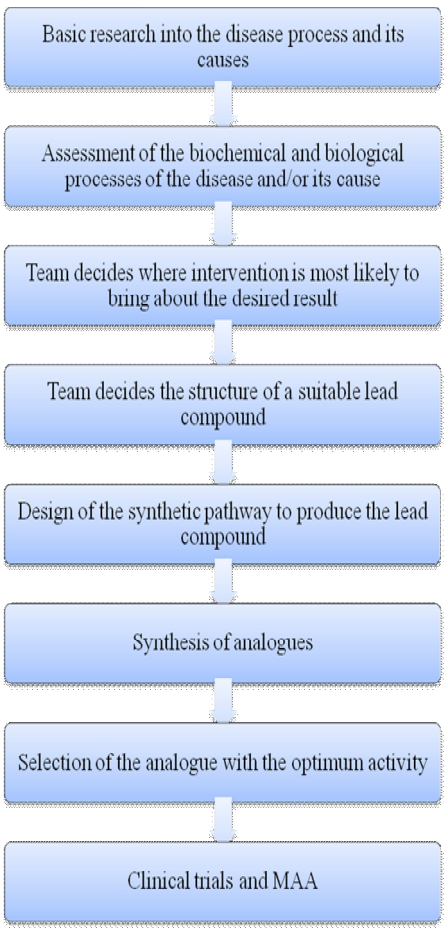


Fig. showing the general steps in the discovery of a new drug for a specific disease state

DRUG DISCOVERY AND DEVELOPMENT

The process of drug discovery and development can be broadly categorized into two subclasses: drug discovery and drug development. The drug discovery process can be described as the identification and validation of a disease target and the discovery and development of a chemical compound to interact with that target[3]. This interaction can be to block, promote or otherwise modify the activity of the

target. Drug development involves satisfying all requirements that have to be met before a new compound can be deemed ready for testing in human subjects for the first time. Drug testing is achieved by preclinical and clinical trials. Currently, the research and development cost of each molecular entity is approximately US $1.8 billion[4]. A number of studies have tried to estimate the cost the most quoted figures being those from the US Pharmaceutical Manufacturers Association (PhRMA) which are based on work done by DiMasi and others at the Tufts Center in Boston[5, 6].

Drug Discovery Pipeline

The process by which a new drug is brought to market stage is referred to by a number of names – most commonly as the development chain or "pipeline"[7].

The process of drug discovery takes about 15 years to complete, and the interesting feature is that it is complete only for few drug candidates as large number of parameters has to follow in order to pass from each and every step.

TARGET IDENTIFICATION – DISEASE MECHANISM

The disease mechanism defines the possible causes of a particular disorder, as well as the path or phenotype of the disease. Targets are the specific components naturally existing cellular or molecular structure involved in the pathology which are responsible for disease; they may be receptors, enzymes, nucleic acids, hormones, ion channels etc. Target selection by the pharmacist depends on the disease on which he focused. Presently, G-protein coupled receptors (GPCR) are the predominant families addressed and more than 600 genes encoding GPCR have been identified. In humans, GPCR are responsible for about 30 disease including Diabetes insipedus, hypo and hyperthyroidism, retinis pigmentosa, several fertility disorders and even carcinoma[8]. Approximately, 150 GPCRs found in human have unknown function[9].

For the identification of target, In Silica approach is widely used, it's a computer based technique to study the specific chemical responses in the body or target organism and tailoring combination of these to fit a treatment profile[10]. Molecular Docking and Scoring techniques are also widely used; it involves computationally placing a virtual molecular structure into a binding site of a biological macromolecule. Various software's have been developed-AutoDock, Zdock, Dock & Docking Server .

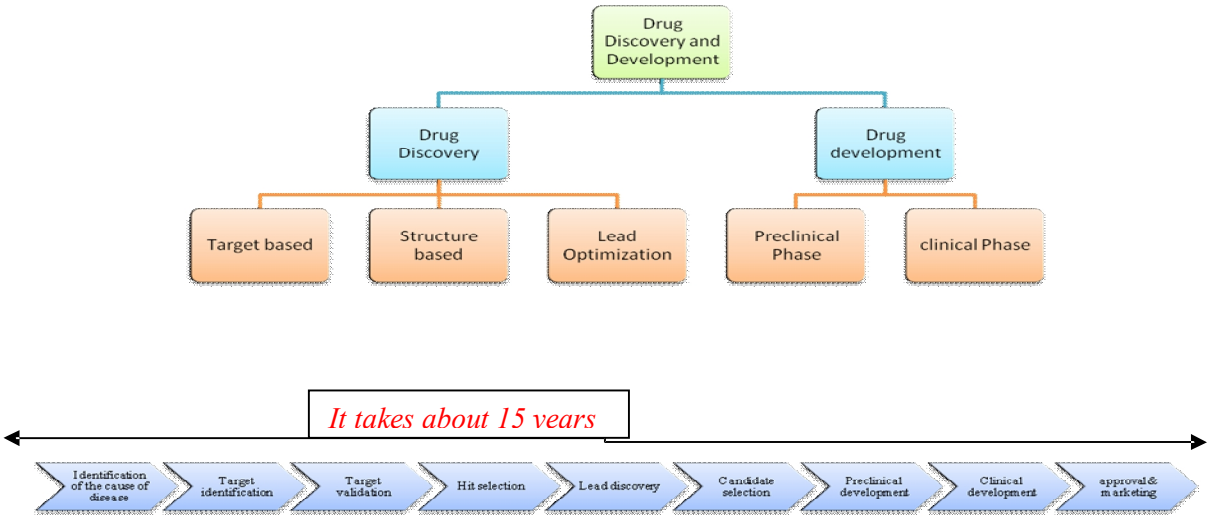


Fig 1. showing the drug discovery pipeline and reveals that how different processes are interlinked.

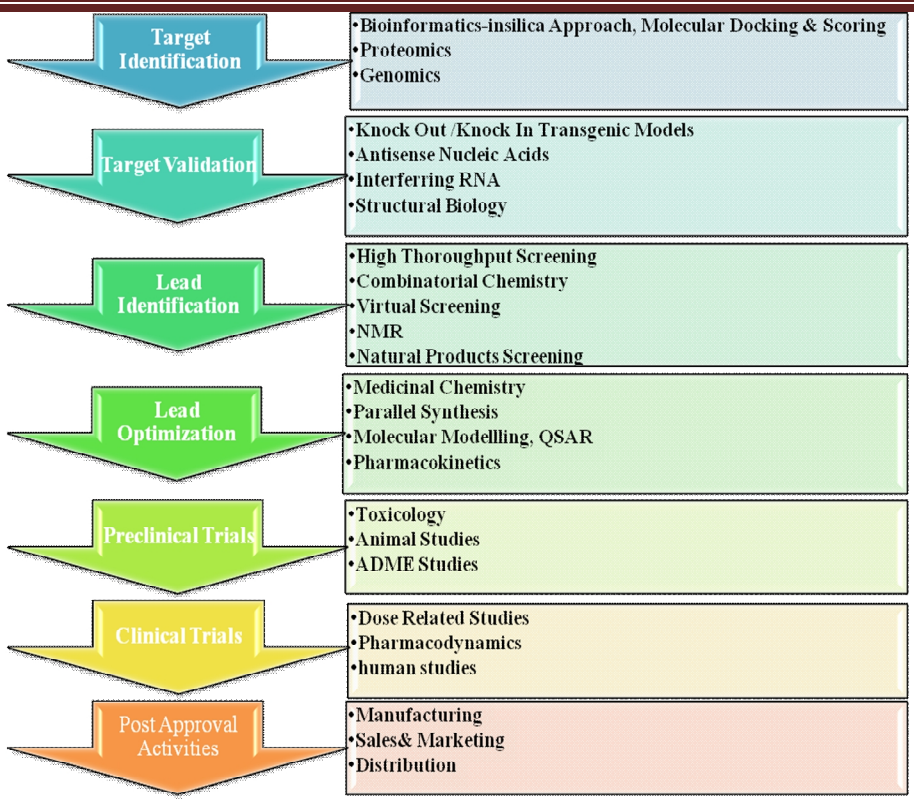


Figure-2: Showing the involvement of different topics and branches of science in various steps of drug discovery

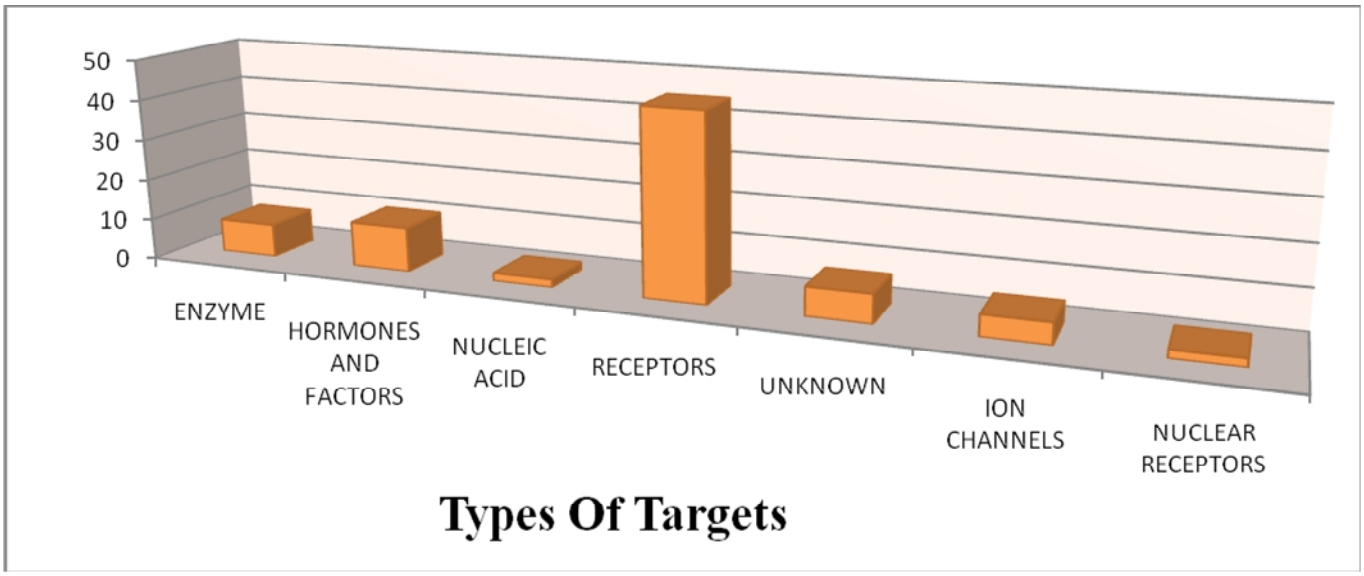


Figure-3 showing different types of targets involving in disease with their percentage

TARGET VALIDATION

It involves demonstrating relevance and confirmation of the target protein in a disease process. Target validation requires a demonstration that a molecular target is critically involved in a Disease process and that modulation of the target is likely to have a therapeutic effect.

In this regard transgenic models are used, one with the target (knock in/gain of function) and another without the target (knock out/loss of function) and with these models validation of target is performed. Knock in is used to develop diseased model and Sometime knock in models are fatal and lead to death. Various neurodegenerative disease models have been generated by introducing mutant genes that cause autosomal-dominant forms of the disease in humans [11].

Antisense DNA/RNA and RNAi may be used; they are oligonucleotides which are complementary to a specific sequence of RNA or DNA. The basic concept of antisense therapeutics is that the antisense compound binds to the native target to form a double-stranded sequence and thus inhibits its actual function. An antisense drug for viral retinitis has been approved. Interfering RNA or RNAi is a gene silencing phenomenon, whereby specific double-stranded RNAs (dsRNAs) trigger the degradation of homologous messenger RNA (mRNA). The specific dsRNAs are processed into small interfering RNA (siRNA), which initiates the cleavage of the homologous mRNA in a complex named the RNA-induced silencing complex (RISC).

After identifying the mechanism of the diseases it leads to the formulation of the drug compound which shows interaction with the target.

HIT TO LEAD SELECTION

Early drug discovery involves several phases from target identification to preclinical development. The identification of small molecule modulators of protein function and the

process of transforming these into high-content lead series are key activities in modern drug discovery[12]. Most commonly hit compounds are derived by High-Throughput Screening (HTS). HTS a high-tech approach for drug discovery in current trend to show how selective the compounds are for the chosen target, and it is more and more gaining popularity among industrial researchers[13]. It is a robust assay that leads to rapid identification of true hits. An assay performed in a 96- or 384-well plate allows researchers to screen many compounds simultaneously. Typical HTS programs have potentials to screening up to10000 compounds per day, while some laboratories with Ultra High-Throughput Screening (UHTS) can perform 100,000 assays per day[14]**.** In addition, once a library of compounds has been established, the same library can be run through many different assays. The quality of assay results is dependent on the assay method(s) and the compounds in the library, so a poorly designed assay or a limited library may result in false hits or miss viable candidates. In practice, because HTS places a premium on rapid assays, false positive and false negative are not uncommon; besides when a true hit is found it is most likely be refined to increase its binding affinity or to change its pharmacological properties (specificity, solubility, stability, kinetic, etc.). This process is called hit-to-lead development.

Recently, techniques like Particle count measurements for varying sample concentration, 2D fluorescence intensity distribution analysis for fluorescence interference[13] or color quenching corrections in scintillation proximity assays (SPAs) have been proposed to eliminate some artifacts[15].

The Probability for effectiveness can be enhanced by applying LIPINSKI RULE[16]**.**

The substance should have a molecular weight of 500 or less.

It should have fewer than five hydrogen-bond donating functions.

It should have fewer than ten hydrogen-bond accepting functions.

The substance should have a calculated log P (c Log P) between approximately −1 to +5.

The important sources for hit/lead compounds are-

i. Local folk remedies (Ethnopharmacology)[17]**.**
ii. By serendipitously discovered (Penicillin, Minoxidil, cisplatin etc.).
iii. by structure-activity relationships.
iv. by rational drug design.
v. High-throughput screening of compounds.
vi. Databases and other literature sources of organic compounds.

LEAD OPTIMIZATION

It follows the lead finding process. The aim of lead optimization to synthesize lead compounds, new analogs with improved potency, reduce off-target activities, as well as to optimize this with respect to other properties viz. selectivity, metabolic stability, etc. This optimization is accomplished through chemical modification of the hit structure, with modifications chosen by employing structure-activity analysis (SAR) as well as structure-based design if structural information about the target is available[18]**.**

The lead compound should have a good druglikeness & would not interfere with the cytochrome P450 enzymes or with the P-glycoproteins.

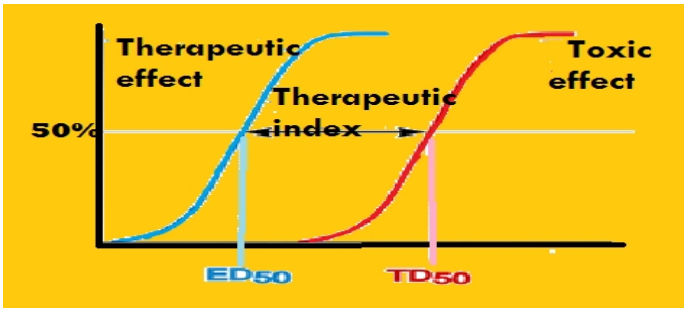
DRUG DEVELOPMENT

Once a new chemical identity is discovered it has to be subjected to the developmental process. Chemical synthetic ability is mostly carried out in the R & D divisions of the pharma companies. The structure activity relationships (SAR) are determined. The study of the promising compound can be divide into two stages-**preclinical pharmacology** (animal studies) and **clinical pharmacology** (human studies).

PRECLINICAL EVOLUTIONS (ANIMAL STUDIES)

The candidate drug is subjected to extensive pharmacological testing invitro and invivo on animal models (mice, rats, pigs, dogs). Major areas of research are[19]:

1. Acute, Subacute and Chronic Toxicity studies (toxicity profile)
2. Therapeutic Index (safety and efficacy evolution): it is the ratio of median lethal dose (LD50) for a drug to the median effective dose (ED50).
3. Absorption, Distribution, Metabolism & Elimination ADME studies (Pharmacokinetics)



CLINICAL STUDIES

These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on efficacy. About 90% of drug candidate entering into clinical trials were failed. In 1991, the main reason for failure was problems in PK/bioavailability (40 %) followed by lack of efficacy (30 %) and toxicology (12 %). In 2000, the main reason for failure was lack of efficacy (27 percent), followed by commercial and market reasons (21 %) and toxicology (20 %)[20]. There are four phases of clinical trials:

PHASE 1: CLINICAL PHARMACOLOGICAL EVOLUTION

Phase 1 usually open study (non – blind) Small number of healthy volunteers (20 – 80). These studies are mainly concerned with human toxicity, tolerated dose range, Pharmacokinetics (ADME characteristics) and Pharmacodynamics which includes mechanism of action as well as dose related effects[21]**.**

PHASE 2: CONTROLLED CLINICAL EVOLUTION

Phase 2 studies carried in groups of patients usually (100 – 300) in number, designed to ascertain the safety and efficacy of new drug, and are strictly controlled. It may include different groups of patients, e.g. Anxiety, depression, phobias, etc. to test therapeutic indication and dose of test compound.

PHASE 3: EXTENDED CLINICAL EVOLUTION

Phase 3 studies are expanded, controlled, and uncontrolled trials. They are performed after preliminary evidence of effectiveness has been obtained in Phase 2. These are formal therapeutic trials carried out Multicentre (1000 – 3000 patients) in a double blind, randomized, placebo controlled manner. The Newly formed drug compared to alternatives. Good Clinical Practice guidelines followed which controls all aspects of conduct of clinical trials (selection, ethics, data collection, methods, and record of info, statistics, and documentation). After phase 3 studies both the sponsor and

drug control authority are satisfied and it is approved for marketed for general use.

PHASE 4: SURVEILLANCE DURING POST MARKETTING GENERAL CLINICAL USE

After the drug is released for general clinical use, certain unusual type of adverse reaction may be observed even after years of clinical usage. Thus an adverse reaction monitoring is carried out in phase 4 evaluation and this continues till the drug is used.

RECENT TECHNIQUES

Computer-aided drug design (CADD) is a specialized discipline that uses computational methods to simulate drug receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases. As such, there is considerable overlap in CADD research and bioinformatics. There are several key areas in bioinformatics regarding CADD research.

CONCLUSION

Since 1990s, the drug discovery process has been revolutionized with the introduction of some newer techniques in molecular biology, biotechnology, genomics, and bioinformatics. Very High expectations from newer trends in drug discovery due to its speed, cost, and greater success. High Throughput Screening (HTS) is a powerful technique which speedup the screening process. Target oriented development is a plus point, and receptors especially G-protein coupled receptors (GPCRs) has been successfully targeted. Despite all this, there has been a steady decline in the number of new drugs and still drug discovery a lengthy, expensive, difficult and inefficient process with low rate of new therapeutic discovery.

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