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An Insight to Drug Designing by *In Silico* approach in Biomedical Research

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Abstract
Drug discovery process basically is a patient oriented science, where researchers strive to improve the existing drugs or invent a totally new chemical entity, which should be ideally more potent than any existing drug of a similar category. The development of new drugs with potential therapeutic applications is one of the most complex and difficult process. Millions of capital and man-hours are devoted to the discovery of new therapeutic agents. Intervention of computers at some plausible steps is imperative to bring down the cost and time required in the drug discovery process. *In Silico* drug designing is a form of computer-based modeling whose technologies are applied in drug discovery processes. This approach has given tremendous opportunity to identify many new potential drugs than the conventional approaches. This article provides an insight to various steps involved the Drug Designing process.
Keywords: Drug Designing, *In Silico*, Molecular Modeling, Drug Discovery

Introduction

Drugs are essential for the prevention and treatment of disease. Human life is constantly threatened by many diseases. Therefore, ideal drugs are always in great demand. To meet the challenges of ideal drugs, an efficient method of drug development is demanding. But the process of drug design, development and commercialization is a tedious, time-consuming and cost-intensive process[1]. To fulfill these challenges, several multidisciplinary approaches are required for the process of drug development; collectively these approaches would form the basis of *In Silico* approach in drug design.

A drug target is a biomolecule which is involved in signaling or metabolic pathways that are specific to a disease process. Biomolecules play critical roles in disease progression by communicating through either protein-protein interactions or protein-nucleic acid interactions leading to the propagation of signaling events and/or alterations of metabolic processes. Therefore, modulation of biological functions performed by these biomolecules would be potentially beneficial and could be achieved either

i) by inhibiting their function with small molecules whose competitive binding affinity would be greater than their natural ligands that bind to the active sites or

ii) by inhibiting the bio molecular interactions (between the biomolecules) by small molecules or

iii) by activating bio molecules that are functionally deregulated in some disease such as cancer[2].

Developing a lead molecule and an effective drug is challenging even for known targets. Recently, drug discovery has significantly increased due to the availability of 3D X-ray or NMR structures of biomolecules, docking tools, and the development of computer aided methodologies [3, 4]. Considering both the potential benefits to human health and the enormous costs in time and money of drug discovery, any tool or technique that increases the efficiency of any stage of the drug discovery enterprise will be highly prized. *In Silico* drug designing is one of these tools which can be used to increase the efficiency of the drug discovery process. This approach cannot maximize its utility alone; rather it can form a valuable partnership with the experimentalist. It provides valuable information and helps to guide further experimental planning and potentially makes this process more efficient.

Methods :

In Silico Drug Designing process comprises of 3 major stages (Fig 1)

Stage 1: It involves identification of therapeutic target and building a heterogeneous small molecule library to be tested against it. This is followed by the development of a virtual screening protocol initialized by docking of small molecules from the library.

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Stage 2: These selected hits are checked for specificity by docking at binding sites of other known drug targets.

Stage 3: These selected hits are subjected to detail *In Silico* ADMET profiling studies and those molecules that pass these studies are termed as leads.

Target Identification

Target identification is the first key stage in the drug discovery pipeline. However, identification of drug able targets form among thousand of candidate macromolecules is still a challenging task. This can be achieved by extensive literature referring, pathway analysis and also by Genomic and proteomic approaches for examples by comparison of the protein expression profiles [5].

Target Validation

After a drug target has been identified, a rigorous evaluation needs to occur to demonstrate that modulation of the target will have the desired therapeutic effect. Target validation process includes determining if the modulation of a target's function will yield a desired clinical outcome. *In Silico* characterization can be carried by using approaches such as genetic-network mapping, protein-pathway mapping, and protein-protein interactions [6].

Lead Discovery

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. Lead can be identified by one or more of several technology-based approaches like structure-based design, virtual High-Throughput screening, literature and patent-based innovations [7].

Lead Optimization

Lead optimization is the complex, no-linear process of refining the chemical structure of confirmed Lead molecules to improve its drug characteristics with the goal of producing drug candidate. Lead structures are optimized for target affinity and selectivity. Docking techniques are currently applied to aid this process [8].

***In Silico* ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) Prediction**

Studies indicate that poor pharmacokinetics and toxicity are the most important causes of costly late stage failures in drug development and it has become widely appreciated that these areas should be considered as early as possible in the drug discovery process. With use of *In Silico* tools it is possible to predict the most relevant pharmacokinetics, metabolic and toxicity endpoints, there by accelerating the drug discovery process [9].

Pre-clinical Studies

The purpose of pre-clinical studies is to provide information on safety and efficacy, in order to begin clinical studies in humans. The discovered drug candidate needs to be validated on a disease-specific animal model to provide experimental proof of concept. The information from pre-clinical studies includes; data on acute toxicity, the kinetics and metabolism of the drug, organ sensitivity and most importantly, a starting dose with an acceptable margin of safety so that there is minimal chance of endangerment to human study subjects [10].

Clinical Studies

The next stage after preclinical studies is the clinical studies, actual testing of the molecule in the human volunteers. This phase allows assessing the safety and efficacy of the new molecule. This phase also allows gathering information about the toxicological effects in the human body. Before the start of this stage, the innovator should file an application for the approval. [7]

Investigational New Drug (IND), as the FDA approves based on the preclinical data, the innovator can proceed for clinical studies [10].

Conclusion

The Drug Designing and development process is a long and expensive one. Due to the limitation of throughput, accuracy and cost, experimental techniques cannot be applied widely; therefore, recently the drug discovery process has shifted to *In Silico* approaches such as homology modeling, protein-ligand interactions, vHTS etc. *In Silico* approach has been of great importance to develop fast and accurate target identification and prediction method for the discovery.

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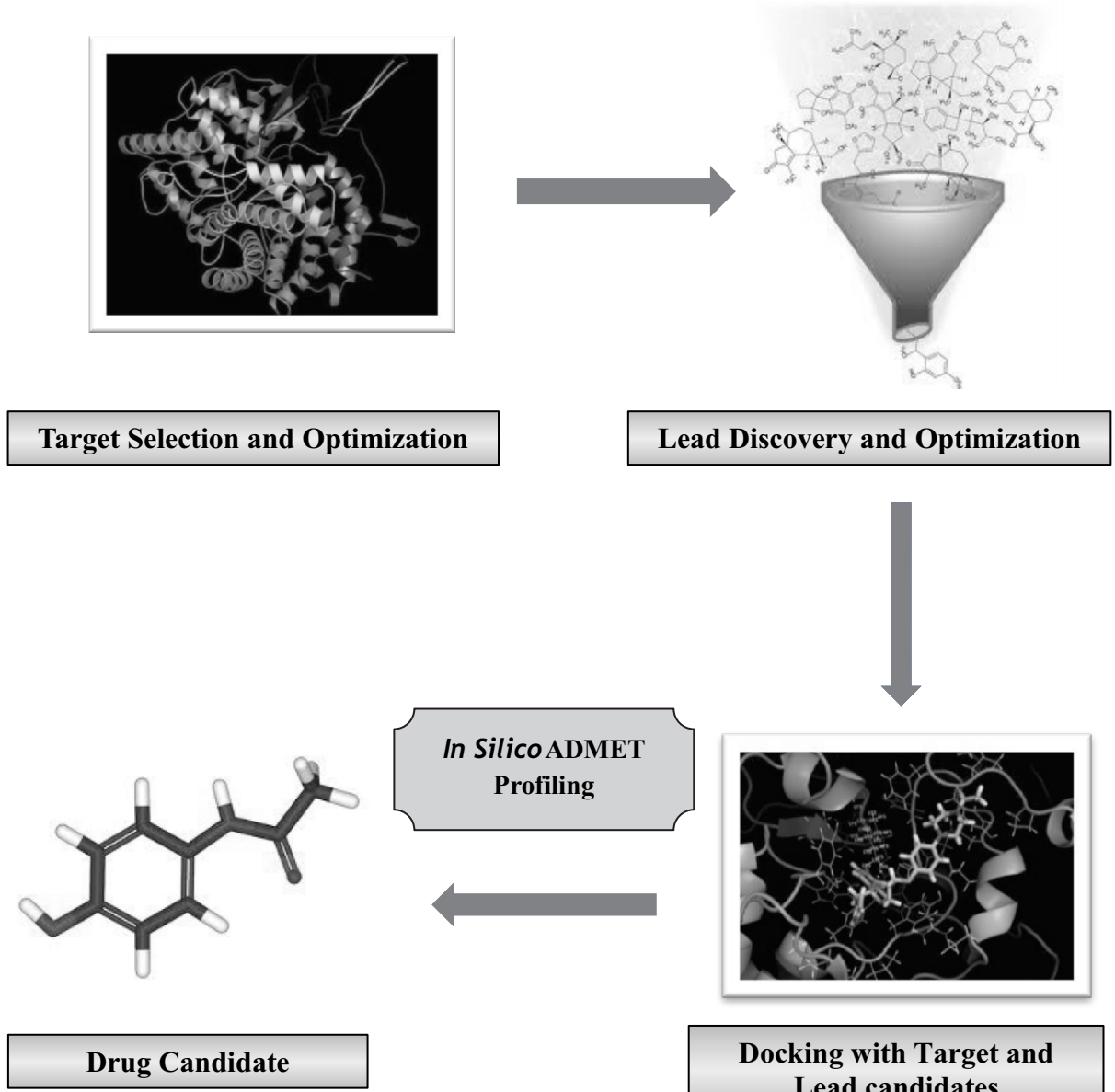
Fig 1: Drug Discovery Process by *In Silico* approach



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