DRUG DEVELOPMENT IN RELATION TO SPECIFIC TARGETS: OPPORTUNITIES AND FUTURE PROSPECTS

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ABSTRACT

Drug is active pharmaceutical ingredient which is a chemical substance of known structure with a certain pharmacological action used to diagnose, cure, treat or prevent the disease. It produces a significant biological effect when administrated to a human being. Natural drugs act as the back bone for humankind in all over the world. As the population increases day by day, the number of new diseases also increases so the new medicines and remedies are also required. Drug design is the creative process to find out the new remedies based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. Generally drug design involves the design of molecules which are complementary in shape and charge to the bio molecular target with which they interact and bind to it in efficient manner. Drug design provides the knowledge of the three-dimensional structure of the bio molecular target. This is known as structure-based drug designing. A bio molecular target most commonly a protein or a nucleic acid is a key molecule involved in a particular metabolic or signalling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. Potential drug targets are not necessarily disease causing but must by definition be disease modifying. In some cases, small molecules will be designed to enhance or inhibit the target function in the specific disease modifying pathway. Small molecules for receptor agonists, antagonists, agonists,or modulators;enzyme activators or inhibitors;ionchannel openers or bl ockers will be designed that are complementary to the binding site of target. A particular example of rational drug design involves the use of three-dimensional information about biomolecules obtained from such techniques as X-ray crystallography and NMR spectroscopy. Computer-aided drug design in particular becomes much more tractable when there is a high-resolution structure of a target protein bound to a potent ligand. Many therapeutic drugs have undesired properties that may become pharmacological, pharmaceutical, or pharmacokinetic barriers in clinical drug application. The present study shows that modulation of target is an important means of improving drug efficacy.

Key Words: SiRNA, RISC, Drug design, Biological target, Nucleic acid, Rational drug discovery.

DRUG DESIGN

Drug designing is very inventive and demandable process of finding new medications based on the knowledge of a biological target [1]. Nowdays computer techniques are very useful in drug designing [2,3]. This type of modeling is sometimes referred to as computer-aided drug design. In addition to small molecules, biopharmaceuticals including peptides [4,5] and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed[6].

Drug design is not a correct phrase but a misnomer upto some extent. A more accurate term is ligand design i.e., design of a molecule that will bind tightly to its target[7]. Although design techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, side effects, etc., that first must be optimized before a ligand can become a safe and efficacious drug. These other characteristics are often difficult to predict with rational design techniques. Nevertheless, due to

high attrition rates, especially during clinical phases of drug development, more attention is being focused early in the drug design process on selecting candidate drugs whose physicochemical properties are predicted to result in fewer complications during development and hence more likely to lead to an approved, marketed drug[8]. Furthermore, in vitro experiments complemented with computation methods are increasingly used in early drug discovery to select compounds with more favourable phenomenon like absorption, distribution, metabolism, excretion and toxicological profiles [9].

DRUG TARGET

A biomolecular target generally it may be a a protein or a nucleic acid, is a key molecule involved in a particular metabolic or signaling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. Potential drug targets are not necessarily disease causing but must by definition be disease modifying [10]. In some cases, small molecules will be designed to enhance or inhibit the target function in the specific disease modifying pathway. Due to similarities in binding sites, closely related targets identified through sequence homology have the highest chance of cross reactivity and hence highest side effect potential.Most commonly, drugs are organic small molecules produced through chemical synthesis, but biopolymer-based drugs (also known as biopharmaceuticals) produced through biological processes are becoming increasingly more common [11]. In addition, mRNA-based gene silencing technologies may have therapeutic applications[12].

RNA molecules are crucial for delivering cellular information and genetic regulation, but until recently, the drug discovery world has emphasized protein drug targets. Our lack of knowledge in RNA biology prevented us from exploring possibilities of RNA drug targets, but with recent advances in technologies such as sequencing, new therapeutic strategies are being explored. To understand RNA-small molecule druggability, we have validated an affinity-selection mass spectrometry screening system for detection of RNA-small molecule interactions. This system was used to screen a variety of RNA targets against diverse small molecule collections, functionally annotated compounds, and collections enriched in RNA-binding properties. The system generated a large dataset of small molecule-ncRNA interactions. RNA plays critical roles in gene expression and regulation and, as such, RNA molecules are implicated human disease, often via the undruggable proteins expressed by those RNAs. RNA as a therapeutic target has been validated clinically by oligonucleotide drugs although with limitations. Recent advances in RNA structure and biology point to the exciting potential of directly targeting RNA with drug-like small molecules, offering potential advantages over oligonucleotides. The past twenty years have seen an explosion of

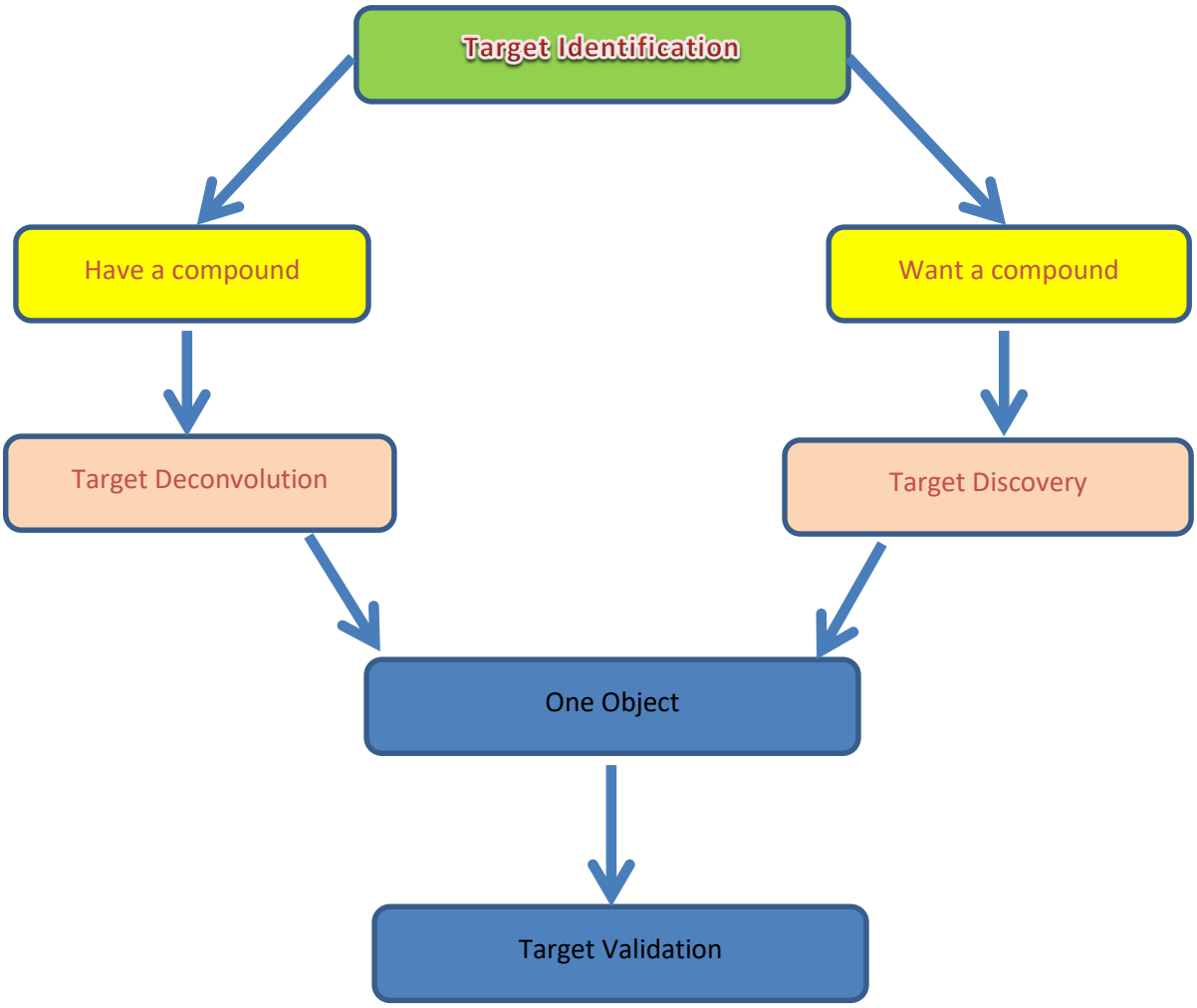

Fig.1 Target Validation process

interest in the structure and function of RNA and DNA. While some 80% of the human genome is transcribed into RNA, just ~3% of those transcripts code for protein sequences. RNA and DNA can be targeted with drug-like small molecules using a Small Molecule Microarray (SMM) screening platform and the molecular basis for these interactions. Small interfering RNAs (siRNAs) that silence genes of infectious diseases are potentially potent drugs. A continuing obstacle for siRNA-based drugs is how to improve their efficacy for adequate dosage. To overcome this obstacle, the interactions of antiviral siRNAs, tested *in vivo*, were computationally examined within the RNA-induced silencing complex (RISC). Thermodynamics data reveals that a persistent RISC cofactor is significantly more exothermic for effective antiviral siRNAs than their ineffective counterparts. Viral RNA secondary structures studies reveal that effective antiviral siRNAs target hairpin or pseudoknot loops. These structures are critical for initial RISC interactions since they partially lack intramolecular complementary base pairing. Importing two temporary RISC cofactors from magnesium-rich hairpins or pseudo knots then kick starts full RNA hybridization and hydrolysis [13].

RATIONAL DRUG DISCOVERY

In contrast to traditional methods of drug discovery (known as forward pharmacology), which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design (also called reverse pharmacology) begins with a hypothesis that modulation of a specific biological target may have therapeutic value. In order for a biomolecule to be selected as a drug target, two essential pieces of information are required. The first is evidence that modulation of the target will be disease modifying. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states [14]. The second is that the target is "druggable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule [15].

Once a suitable target has been identified, the target is normally cloned and produced and purified. The purified protein is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.

The search for small molecules that bind to the target is begun by screening libraries of potential drug compounds. This may be done by using the screening assay (a "wet screen"). In addition, if the structure of the target is available, a virtual screen may be performed of candidate drugs. Ideally the candidate drug compounds should be "drug-like", that is they should possess properties that are predicted to lead to oral bioavailability, adequate chemical and metabolic stability, and minimal toxic effects [16]. Several methods are available to estimate druglikeness such as Lipinski's Rule of Five and a range of scoring methods such as lipophilic efficiency [17]. Several methods for predicting drug metabolism have also been proposed in the scientific literature [18].

Due to the large number of drug properties that must be simultaneously optimized during the design process, multi-objective optimization techniques are sometimes employed [19]. Finally because of the limitations in the current methods for prediction of activity, drug design is still very much reliant on serendipity [20] and bounded rationality [21]. This approach to drug discovery is sometimes referred to as structure-based drug design. The first unequivocal example of the application of structure-based drug design leading to an approved drug is the carbonic anhydrase inhibitor dorzolamide, which was approved in 1995 [22,23].

Another important case study in rational drug design is imatinib, a tyrosine kinase inhibitor designed specifically for the *bcr-abl* fusion protein that is characteristic for Philadelphia chromosome-positive leukemias (chronic myelogenous leukemia and occasionally acute lymphocytic leukemia). Imatinib is substantially different from previous drugs for cancer, as most agents of chemotherapy simply target rapidly dividing cells, not differentiating between cancer cells and other tissues [24]. Finding novel, druggable targets for therapeutic intervention remains a top priority for the pharma and biotech industry. It also remains a formidable challenge and companies continue to invest a lot of time and resources in identifying and validating targets that will yield viable drugs. What are the challenges in target discovery today? What new tools and strategies are being used to identify targets and how well are they working? What's being done to adequately validate the targets once they are identified? What efforts are being taken to go after difficult or "undruggable" targets? The tricarboxylic acid cycle intermediate succinate is involved in metabolic processes and plays a crucial role in the homeostasis of mitochondrial reactive oxygen species. The receptor responsible for succinate signalling, SUCNR1 it is also known as GPR91, is a member of the G-protein-coupled-receptor family and links succinate signalling to renin-induced hypertension, retinal angiogenesis and inflammation. SUCNR1 senses succinate as an immunological danger signal which has relevance for diseases including ulcerative colitis, liver fibrosis, diabetes and rheumatoid arthritis. It is of interest as a therapeutic target. Structure-based mutagenesis and radio ligand-binding studies, in conjunction with molecular modelling, identified key residues for species-selective antagonist binding and enabled the determination of the high-resolution crystal structure of a humanized rat SUCNR1 in complex with a high-affinity, human-selective antagonist denoted NF-56-EJ40.
Calcineurin is important for fungal virulence and a potential antifungal target, but compounds targeting calcineurin, such as FK506, are immunosuppressive. Here we report the crystal structures of calcineurin catalytic (CnA) and regulatory (CnB) subunits complexed with FK506 and the FK506-binding protein (FKBP12) from human fungal pathogens (*Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans* and *Coccidioides immitis*). Fungal calcineurin complexes are similar to the mammalian complex, but comparison of fungal and human FKBP12 (hFKBP12) reveals conformational differences in the 40s and 80s loops. NMR analysis, molecular dynamic simulations, and mutations of the *A. fumigatus* CnA/CnB-FK506-FKBP12-complex identify a Phe88 residue, not conserved in hFKBP12, as critical for binding and inhibition of fungal calcineurin. These differences enable to develop a less immunosuppressive FK506 analog, APX879, with an acetohydrazine substitution of the C22-carbonyl of FK506. APX879 exhibits reduced immunosuppressive activity and retains broad-spectrum antifungal activity and efficacy in a murine model of invasive fungal infection [26].

COMPUTER AIDED DRUG DESIGN

The most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics is most often used to estimate the strength of the intermolecular interaction between the small molecule and its biological target. These methods are also used to predict the conformation of the small molecule and to model conformational changes in the target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods,

or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity [27].

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets [28,29] or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target [30,31].

Ideally, the computational method will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. The reality is that present computational methods are imperfect and provide, at best, only qualitatively accurate estimates of affinity. In practice it still takes several iterations of design, synthesis, and testing before an optimal drug is discovered. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures [32,33].

Drug design with the help of computers may be used at any of the following stages of drug discovery. The first stage is hit identification using virtual screening as in structure or ligand-based design. The second stage is hit-to-lead optimization of affinity and selectivity which is also structure based. The third stage is lead optimization of other pharmaceutical properties while maintaining affinity.

LIGAND BASED DRUG DESIGN

Ligand-based drug design (or **indirect drug design**) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target [34]. In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs [35].

STRUCTURE BASED DRUG DESIGN

Structure-based drug design (or **direct drug design**) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy [36]. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively various automated computational procedures may be used to suggest new drug candidates [37].

Current methods for structure-based drug design can be divided roughly into three main categories [38]. The first method is identification of new ligands for a given receptor by searching large databases of 3D structures of small molecules to find those fitting the binding pocket of the receptor using fast approximate docking programs.

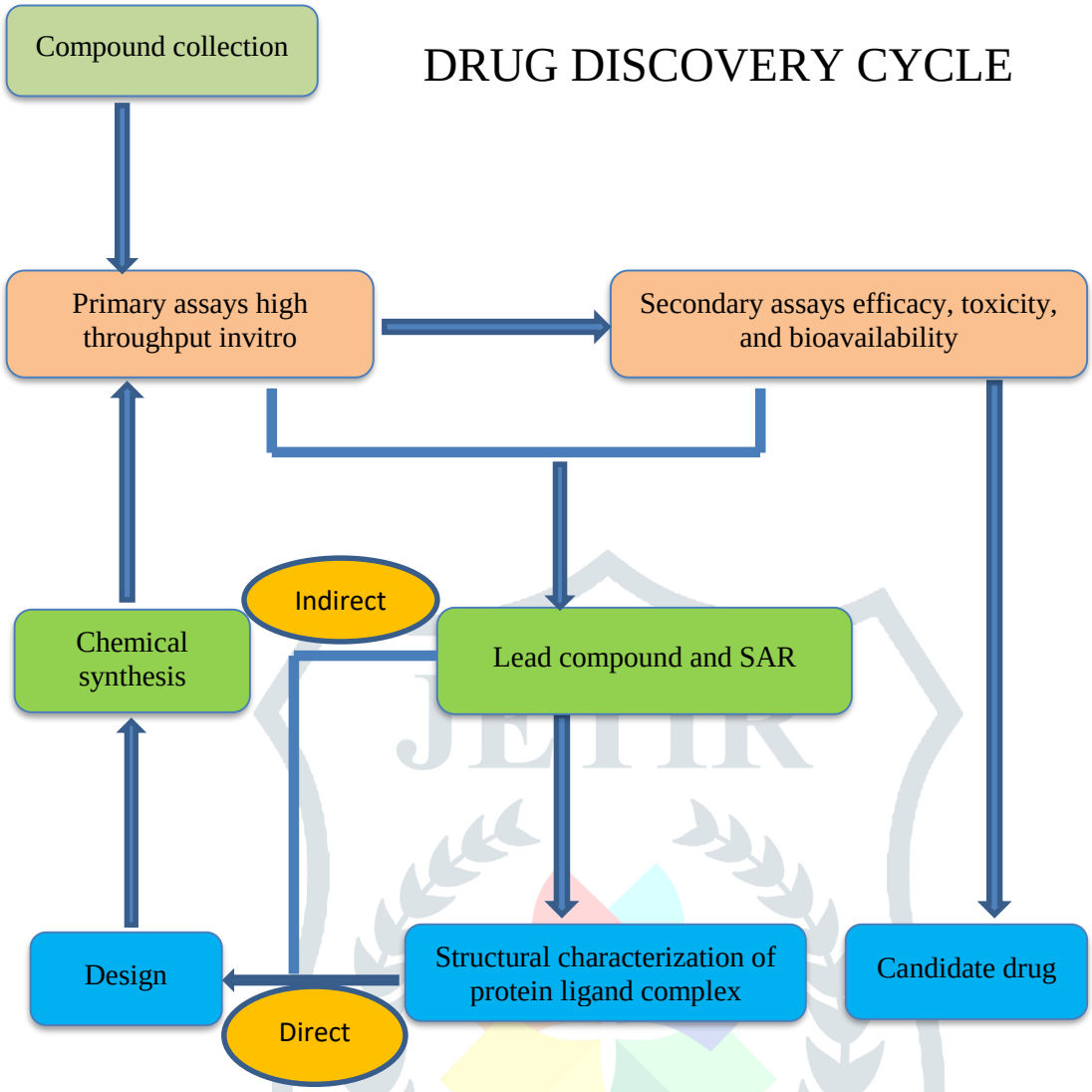

Fig.1 Drug discovery cycle showing structure-based and ligand-based drug design strategies.

This method is known as virtual screening. A second category is de novo design of new ligands. In this method, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures, not contained in any database, can be suggested [39,40,41]. A third method is the optimization of known ligands by evaluating proposed analogs within the binding cavity [38].

Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying the molecular recognition. Selective high affinity binding to the target is generally desirable since it leads to more efficacious drugs with fewer side effects. Thus, one of the most important principles for designing or obtaining potential new ligands is to predict the binding affinity of a certain ligand to its target and also known as antitarget. This predicted affinity may be used as a criterion for selection [42].

BINDING SITE IDENTIFICATION

Binding site identification is the first step in structure based design. If the structure of the target or a sufficiently similar homolog is determined in the presence of a bound ligand, then the ligand should be observable in the structure in which case location of the binding site is trivial. However, there may be unoccupied allosteric binding sites that may be of interest. Furthermore, it may be that only apoprotein (protein without ligand) structures are available and the reliable identification of unoccupied sites that have the potential to bind ligands with high affinity is non-trivial. In brief, binding site identification usually relies on identification of concave surfaces on the protein that can accommodate drug sized molecules that also possess appropriate "hot spots" (hydrophobic surfaces, hydrogen bonding sites, etc.) that drive ligand

binding [17,43]. One early general-purposed empirical scoring function to describe the binding energy of ligands to receptors was developed by Böhm [[44].

ROLE OF FREE ENERGY

The basic idea is that the overall binding free energy can be decomposed into independent components that are known to be important for the binding process. Each component reflects a certain kind of free energy alteration during the binding process between a ligand and its target receptor. Various computational methods are used to estimate each of the components of the master equation. For example, the change in polar surface area upon ligand binding can be used to estimate the desolvation energy. The number of rotatable bonds frozen upon ligand binding is proportional to the motion term. The configurationally or strain energy can be estimated using molecular mechanics calculations. Finally the interaction energy can be estimated using methods such as the change in non-polar surface, statistically derived potentials of mean force, the number of hydrogen bonds formed, etc. In practice, the components of the master equation are fit to experimental data using multiple linear regressions. This can be done with a diverse training set including many types of ligands and receptors to produce a less accurate but more general "global" model or a more restricted set of ligands and receptors to produce a more accurate but less general "local" model [45].

MECHANISM OF DRUG ACTION

In pharmacology, the term mechanism of action (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor [46]. Receptor sites have specific affinities for drugs based on the chemical structure of the drug, as well as the specific action that occurs there.

Drugs that do not bind to receptors produce their corresponding therapeutic effect by simply interacting with chemical or physical properties in the body. Common examples of drugs that work in this way are antacids and laxatives [47].

Drugs can act at four different levels 1. Molecular 2. Cellular 3. Tissue 4. System
The mechanism of drug action can be determined by the help of following methods

1. Microscopy based method Bioactive compounds induce phenotypic changes in target cells, changes that are observable by microscopy, and which can give insight into the mechanism of action of the compound [48].

2**. Direct biochemical method** Direct biochemical methods include methods in which a protein or a small molecule, such as a drug candidate, is labeled and is traced throughout the body. This proves to be the most direct approach to find target protein that will bind to small targets of interest, such as a basic representation of a drug outline, in order to identify the pharmacophore of the drug. Due to the physical interactions between the labeled molecule and a protein, biochemical methods can be used to determine the toxicity, efficacy, and the mechanism of action of the drug [49].

3. Computation inference methods

Typically, computation inference methods are primarily used to predict protein targets for small molecule drugs based on computer based pattern recognition [49]. However, this method could also be used for finding new targets for existing or newly developed drugs.

4. Omics based methods

Omics based methods use omics technologies, such as reverse genetics and genomics, transcriptomics, and proteomics, to identify the potential targets of the compound of interest [50].

Conclusion:
Drug designing is very challenging and inventive field in the current scenario in all over the world. The finding of new remedies based according to the biological target is a very hard job. As the population increases, the new type of diseases, virus, bacteria also increases so the requirement of viable drugs also increases for the sake of healthy human life. In this review we discusses about the principle of drug design, various approaches of drug design ,drug targets, mechanism of drugs and various modification related to various types of drug discovery. Bioisosterism is an important lead modification approach that has been shown to be useful to attenuate toxicity. However process of drug discovery by laboratory experiments is time consuming and very expensive as compared to computational methods. Nowdays computer aided drug

discovery is a very important tool in drug designing. This field provides many new dimensions and opputunities in the field of drug discovery.

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