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Computer Aided Drug Design: The Most Fundamental Goal is to Predict Whether a Given Molecule will Bind to a Target and if so How Strongly

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Abstract
In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it. Drug design, sometimes referred to as rational drug design or more simply rational design is the inventive process of finding new medications 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. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bimolecular target is known as 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. If an experimental structure of a target is not available, it may be possible to create a homology 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.
Keywords: Therapeutic, Three-dimensional structure, Rational drug design, Structure-based drug design, Crystallography and Spectroscopy.

1. INTRODUCTION

The phrase "drug design" is to some extent a misnomer [3]. What is really meant by drug design is ligand design (i.e., design of a small molecule that will bind tightly to its target). Although modeling techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, lack of 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 optimize using rational drug design techniques [5].
Typically a drug target is a key molecule involved in a particular metabolic or signaling pathway that is specific to a disease condition or pathology or to the infectivity or survival of a microbial pathogen. Some approaches attempt to inhibit the functioning of the pathway in the diseased state by causing a key molecule to stop functioning [8]. Drugs may be designed that bind to the active region and inhibit this key molecule. Another approach may be to enhance the normal pathway by promoting specific molecules in the normal pathways that may have been affected in the diseased state [10]. In addition, these drugs should also be designed so as not to affect any other important "off-target" molecules or antitargets that may be similar in appearance to the target molecule, since drug interactions with off-target molecules may lead to undesirable side effects. Sequence homology is often used to identify such risks.
Most commonly, drugs are organic small molecules produced through chemical synthesis, but biopolymer-based drugs (also known as biologics) produced through biological processes are becoming increasingly more common. In addition, mRNA-based gene silencing technologies may have therapeutic applications [16].

2. TYPES

There are two major types of drug design. The first is referred to as ligand-based drug design and the second, structure-based drug design.

2.1 Ligand-based

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. 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 [4]. Alternatively, a quantitive 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.

2.2 Structure-based

As **experimental methods** such as X-ray crystallography and NMR develop, the amount of information concerning 3D structures of biomolecular targets has increased dramatically. In parallel, information about the structural dynamics and electronic properties about ligands has also increased. This has encouraged the rapid development of the structure-based drug design. Current methods for structure-based drug design can be divided roughly into two categories. The first category is about finding ligands for a given receptor, which is usually referred as database searching [6-9]. In this case, a large number of potential ligand molecules are screened to find those fitting the binding pocket of the receptor. This method is usually referred as ligand-based drug design. The key advantage of database searching is that it saves synthetic effort to obtain new lead compounds. Another category of structure-based drug design methods is about building ligands, which is usually referred as receptor-based drug design [11]. In this case, 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.

2.2.1 Active Site Identification

Active site identification is the first step in this program. It analyzes the protein to find the binding pocket, derives key interaction sites within the binding pocket, and then prepares the necessary data for Ligand fragment link. The basic inputs for this step are the 3D structure of the protein and a pre-docked ligand in PDB format, as well as their atomic properties.

The space inside the ligand binding region would be studied with virtual probe atoms of the four types above so the chemical environment of all spots in the ligand binding region can be known. Hence we are clear what kind of chemical fragments can be put into their corresponding spots in the ligand binding region of the receptor.

2.2.2 Ligand Fragment Link

When we want to plant “seeds” into different regions defined by the previous section, we need a fragments database to choose fragments from [8-10]. The term “fragment” is used here to describe the building blocks used in the construction process. The rationale of this algorithm lies in the fact that organic structures can be decomposed into basic chemical fragments. Although the diversity of organic structures is infinite, the number of basic fragments is rather limited.

2.2.3 Scoring Method

Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying accepted principles of molecular recognition. The basic assumption underlying structure-based drug design is that a good ligand molecule should bind tightly to its target. 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 use it as a criterion for selection.

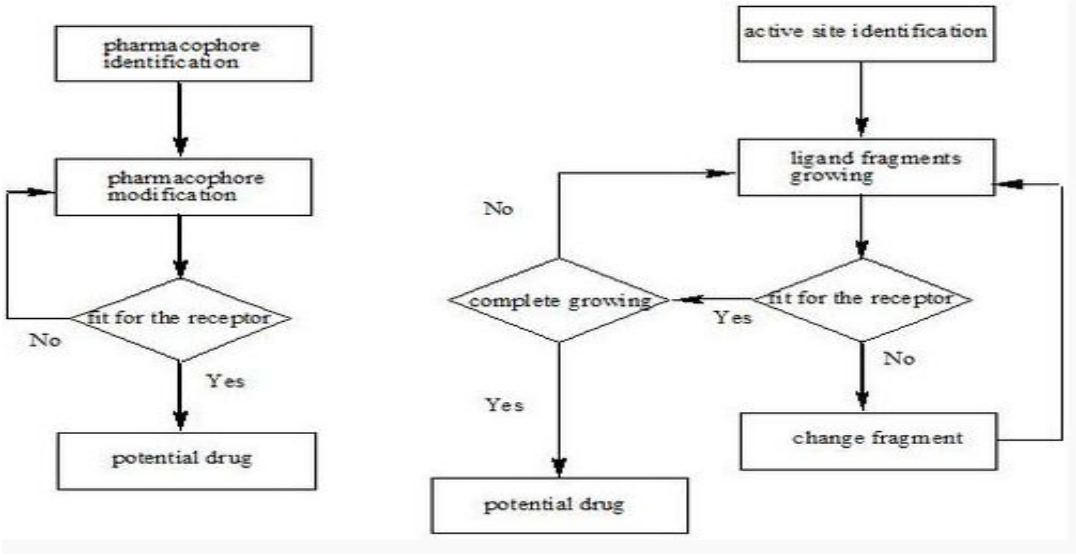

Fig. 2.1 Flow charts of two strategies of structure-based drug design

3. Rational Drug Discovery

In contrast to traditional methods of drug discovery, 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 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 have therapeutic value. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states. The second is that the target is "drugable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

1. Once a suitable target has been identified, the target is normally cloned and expressed. The expressed target is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.
2. 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 [14]. 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. Several methods are available to estimate drug likeness such as Lipinski’s Rule of Five and a range of scoring methods such as lipophilic efficiency. Several methods for predicting drug metabolism have been proposed in the scientific literature, and a recent example is SPORCalc. Due to the complexity of the drug design process, two terms of interest are still serendipity and bound rationality. Those challenges are caused by the large chemical space describing potential new drugs without side-effects.

4. Computer-Aided Drug Design

Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. Molecular mechanics or molecular dynamicsare most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it [7]. Semi-empirical, initio quantum chemistry method, or density functional theroy, 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, polarizabiliyt, etc.) of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring funtion may be used to provide binding affinity estimates [11-13]. These methods use linear regression, machine learing, neural nets 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.

Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized. The reality however is that present computational methods are imperfect and provide at best only qualitatively accurate estimates of affinity. Therefore in practice it still takes several iterations of design, synthesis, and testing before an optimal molecule is discovered. On the other hand, computational methods have accelerated discovery by reducing the number of iterations required and in addition have often provided more novel small molecule structures.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or ligand-based design)
2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
3. lead optimization optimization of other pharmaceutical properties while maintaining affinity

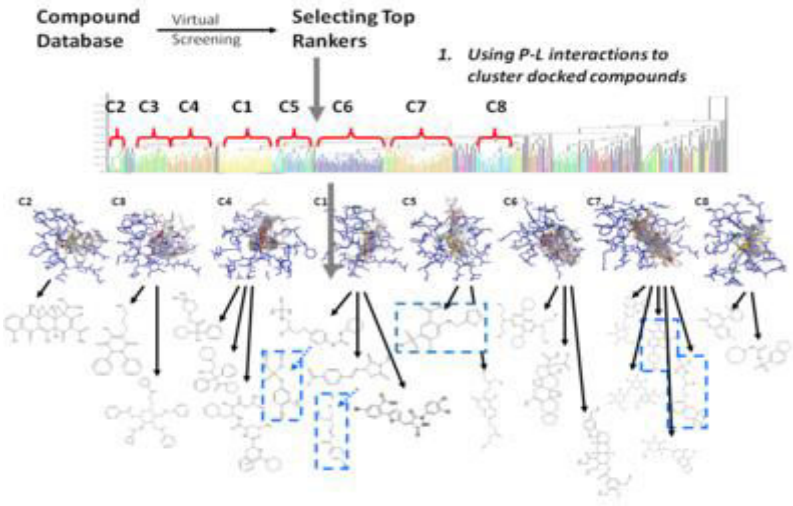

Fig. 4.1 Flowchart of a Usual Clustering Analysis for Structure-Based Drug Design

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used to analysis [17].

5. Conclusion

A particular example of rational drug design involves the use of three-dimensional information about bimolecular obtained from such techniques as X-ray crystallography and NMR spectroscopy [12]. Computer-aided drug design in particular becomes much more tractable when there's a high-resolution structure of a target protein bound to a potent ligand. 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 anhydrate inhibitor dorzalamide, which was approved in 1995.

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 acutelymphocytic 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.

6. References:

[1]. Verlinde CL, Hol WG (July 1994). "Structure-based drug design: progress, results and challenges". Structure 2 (7): 577-87. doi:10.1016/s0969-2126(00)00060-5.PMID 7922037.

[2]. Cohen, N. Claude (1996). Guidebook on Molecular Modeling in Drug Design. Boston: Academic Press. ISBN O-12-178245-X.

[3]. Brown AW and Wallnau KC (Sep 1998). The Current State of CBSE. IEEE Software, 15(5):37–46.

[4]. Wang R,Gao Y,Lai L (Jan 2000). "LigBuilder: A Multi-Purpose Program for Structure-Based Drug

Design". Journal of Molecular Modeling 6 (7–8): 498–516. doi:10.1007/s0089400060498.
[5]. Cai X, Lyu M, Wong K, and Ko R (May 2000). Component-Based Software Engineering: Technologies, Development Frameworks and Quality Assurance Schemes. In APSEC '00: Proceedings of the Seventh Asia-Pacific Software Engineering Conference, 372, Washington, DC, USA. IEEE Computer Society.
[6]. Gohlke H, Hendlich M, Klebe G (January 2000). "Knowledge-based scoring function to predict protein-ligand interactions". J. Mol. Biol. 295 (2): 356. doi:10.1006/jmbi.1999.3371.PMID 10623530.
[7]. Jorgensen WL (March 2004). "The many roles of computation in drug discovery". Science 303(5665):8. Bibcode 2004Sci.303.1813j. doi: 1126/science.1096361.PMID 15031495.
[8]. Schneider G, Fechner U (August 2005). "Computer-based de novo design of drug-like molecules". Nat Rev Drug Discov (8): 649–63. doi:10.1038/nrd1799.PMID 16056391.
[9]. Leach, Andrew R.; Harren Jhoti (Aug 2007). Structure-based Drug Discovery. Berlin: Springer. ISBN 1-4020-4406-2.
[10]. Central Intelligence Agency (Dec 2008). World Fact Book. CIA. Retrieved April 15, 2008 from https://www.cia.gov/library/publications/the-world-factbook/index.html
[11] . de Azevedo WF, Dias R (December 2008). "Computational methods for calculation of ligand-binding affinity". Curr Drug Targets 9 (12): 19. doi:10.2174/138945008786949405. PMID 19128212.
[12]. Microsoft. Windows azure (2011). http://www.microsoft.com/ windowsazure.
[13]. Google. Picasa web albums: free photo sharing from google (2011). http:// picasaweb.google.com.
[14]. Strohl, W.R. (2010), The role of natural products in a modern drug discovery program, Drug Discover Today, 39-41.
[15]. Scharpe, S. and De Meester, I (2011), Peptide truncation by dipeptidyl peptidase IV: a newpathway for drug discovery?, Verh K Acad Geneeskd Belg, 63 5-32; discussion 32-3.
[16]. Ashish Shrivastava, Mickey Sahu, (Febrary 2013) Vol 2, Issue 2. "Computer Abetted Drug Design: New Therapeutic Approach For Development of Target Database". International Journal of Innovative Research & Development. ISSN: 2278.0211.
[17]. Mickey Sahu, Ashish Shrivastava (March-April 2013) Volume 5, Issue 4. "Computer Abetted Drug Design: Application of Drug-target like protein prediction using learning algorithms of support vectore machine". IOSR Journal of Pharmacy and Biological Science (IOSR-JPBS) e-ISSN: 2278-3008.

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