COMPUTER AIDED DRUG DISCOVERY (STRUCTURE-BASED ANDLIGAND-BASED) DESIGN

Supported by tetfund TERTIARY EDUCATION TRUST FUND

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Abstract: Driven by chemistry but increasingly guided by pharmacology and the clinical sciences, drug research has contributed more to the progress of medicine during the past century than any other scientific factor. Computer based drug design is an alternative to the conventional process of drug development. It involves modifying a known drug for new therapeutic indication using computer technology. It has the advantage of being cost effective and time saving. The success in this area are due to identifications of molecular targets, elucidation of 3D structures by X-ray crystallography, NMR, Data availability (for biological targets and ligand) and availability of computer aided software's. Computational drug design can be divided into two, which are structure-based and ligand based. Ligand based makes use of the knowledge of known active and inactive molecules for chemical similarity search or Quantitative Structure-Activity Relation (QSAR). The structured based make use of the knowledge of the target protein structure and is used when the data-base of the crystalline target proteins are available. The ligand based on the other hand is used when the 3D structures of the target proteins are not available.

Keywords: Drugs, discovery, computer, pharmacology, pharmacophore, ligand, structure.

Introduction

Drug research began its career when chemistry had reached a degree of maturity that allowed its principles and methods to be applied to problems in and outside of chemistry itself and when pharmacology has become a well defined scientific discipline in its own right (Drew, 1999). In 1865, August Kekule formulated his pioneering theory on the structure of aromatic organic (molecules). These discoveries lead to research on coal tar derivatives leading to the evolution of dyes. This evolution of dye had a profound influence on medicine; due to the selective affinity of dyes for biological tissues, Paul Ehrlich postulated the existence of chemoreceptors (More, 1989; Roberts, 1989). He argued that certain chemoreceptors on parasites, micro organisms, and cancer cells would be different from analogous structures in host tissues, and that these differences could be exploited therapeutically. It was the birth of chemotherapy, a particular type of drug therapy, which in the course of the 20th Century led to unprecedented therapeutic triumphs (Sertume *et al.,* 1817). Analytical chemistry, in particular the isolation and purification of the active ingredients of medicinal plants, also demonstrated its value for medicine in the 19th century. In 1815, morphine was isolated from opium extract (Sneader, 1985). Also, papaverin was isolated in 1848, but its antispasmodic properties were not discovered until 1917 (Chem *et al.,* 1940). As active ingredients from plants became available, many pharmacists addressed the problem of providing standardized preparation of these often still impure drugs.

In the first half the 20th Century, drug research was shaped and enriched by several new technologies, all of which left their imprint on drug discovery and on therapy. Howard Flory and his colleagues selected penicillin, a metabolite from a penicilliummold that could lyse staphylococci, for further study (Fleming, 1940). Meanwhile penicillin had been discovered in 1929 by Alexander Flemming (Mildrum *et al.,* 1940). Chain and Flory choice to study penicillin turned out to be very fortunate, because it's efficacy and lack of toxicity. Penicillin made the most compelling case for antibiotics in general. It opened the door to a new era in the treatment of bacterial infections. After discovery of penicillin and subsequently of other antibiotics many drug companies established microbiology and fermentation units, which added to their technological scope. Biochemistry influence drug research in many ways. The dominant concepts introduced by biochemistry were those of enzymes and receptors, which were empirically found to be good drug targets. The description and characteristic of carbohydrate in 1933 (Schwartz *et al*., 1945) was fortuitously followed by the discovery that sulphanilamide, the active metabolite of the sulphonamide (sulphadrug) protosil, inhibited this enzyme and that this effect led to an increase in natriuresis and excretion of water (Schwartz *et al*., 1945).

Sulphanalimide gave rise to better carbohydrate inhibitors such as acetazolamide which later led to more efficient diuretics such as hydrochlorothiazide and frusemide (Lewis, 2011). There are structural genealogies that linked sulfonamides like sulfathiazole, with sulfonylureas like tolbutamide, used in the treatment of type II diabetes mellitus, and with diuretics that are being used to treat edema, glaucoma, or essential hypertension. Structural pathways illustrate the fact that the sequential development of different therapeutic areas could well be interpreted as chemical diversification that at first occurred spontaneously. After serendipitous biological findings had seen made, certain prototype structures were further derived in order to obtain compounds with improved or altogether novel effects. The idea of a receptor as a selective binding site for chemotherapeutic agents, first proposed by Paul Erlich has already been mentioned.

Methods of drug discovery

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 are 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. Semi-empirical, 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 (Singh *et al.*, 2003).

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 (Becker *et al.*, 2006; Song *et al*., 2009).

It is estimated that a typical discovery cycle, from lead identification through to clinical trials, can take 14 years with a cost of 800 million US dollars. In the early 1990s, rapid developments in the fields of combinational chemistry and high – throughput screening technologies have created an environment for expediting the discovery process by enabling huge libraries of compounds to be synthesized and screened in short periods of time. However, these concerted efforts not only failed to increase the number of successfully launched new molecular entities, but seemingly aggravated the situation. Among the late stage failures, 40 – 60% was reportedly due to adsoption, distribution, metabolism, excretion and toxicity (ADMETOX) deficiencies. Collectively, these issues underscore the need to develop alternative strategies that can help remove unsuitable compounds before the exhaustion of significant amount of resources (Dodson *et al.*, 1972). The more recent foundations of CADD were established in the early 1970s with the use of structural biology to modify the biological activity of insulin (Beddell *et al*., 1976) and to guide the synthesis of human heamoglobin ligands (Congrene *et al.*, 2005). At that time X-ray crystallography was expensive and time – consuming, rendering it in feasible for large – scale screening in industrial laboratories (Blandell, 1996)

Over the years, new technologies such as comparative modeling based on material structural homologues have emerged and began to be exploited in lead design (Grower S et al 2006). These together with advance in combinatorial chemistry, high – throughput screening technologies and computational infrastructures, have rapidly bridged the gap between theoretical modelling and medicinal chemistry. Numerous successes of designed drugs were reported, including Dorzolamide for the treatment of cystoid macular edema (OvonItzetsin *et al.*, 1993), Zanamir for therapeutic or prophylactic treatment of influenza infection (Tersett *et al.*, 1996). Sidenafil for treatment of male erectile disfunction (Leach *et al.*, 2007) and Amprenavir for treatment of HIV infection.

Brief history of CADD

The history of computer aided drug design can be traced back to 1900s and was pioneered by Paul Ehrich in what was term; "The receptor and lock and key concepts p" (Ehrich, 1909; Fisher, 1894). Then in the 1970s the quantitative structure-activity relationship (QSAR) came into play. The use of modern method of structure determination like X-ray crystallography, multi-dimensions NMR. Molecular modelling computer graphics came into play in the 1980s. Then in the 1990s, the use of human genome, Bioinformatics, Combinatorial chemistry, High throughput screening came to be.

How CADD works

Target identification

Genetics
molecular biology
Bioinformatics

↓

Structure determination

X – ray crystallography
NMR spectroscopy

↓

Biological assays

Molecular modeling
Computer graphics

↓

Synthetic chemistry

Peptidomimetics
Combinational chemistry

↓

Clinical treals

Software for general purpose molecular modelling

This are list of some computer soft wares that are used in modelling for drug discovery.

For work stations, minicomputers, and super computers (SGI, Sun, Cray)

AMBER – Peter Kollman and coworkers, UCSF

Computer assisted model building, energy minimization, molecular dynamics, and free energy perturbation calculations.

Midas plus – UCSF computer graphics Laboratory

CHARMM – Martin karplus and coworkers, (Havard)

QUANTA/CHARM – Molecular Simulations Inc.

Structure Based Drugs 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 (Mauser *et al.*, 2008). 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 (Roberts *et al.*, 1990). During the early 1980s, the ability to rationally design drugs using protein structure was an unrealized goal for many structural biologists. The first projects were underway in the mid-80s, and by the early 1990s the first success stories were published (Roberts *et*

al., 1990). Today even though there is still quite a bit of fine – funning necessary to perfect the process, structure – based drug design is an integral part of most industrial drug discovery programmes (Dorsey *et al*., 1994) and is the major subject of research for many academic laboratories.

The completion of the human genome project, the start of both the proteomics and structural genomics revolution, and developments in information technology are fueling an even greater opportunity for structure based drug design to be part of the success story in the discovery of new drug leads. Excellent drug targets are identified at an increased pace using developments in bioinformatics. The genes for these targets can be cloned quickly, and the protein expressed and purified to homogeneity. Advances in high – through put crystallography, such as automation at all stages, more intense synchrotron radiation, and new developments in phase determination, have shortened the timeline for determining structures. Structure determination using Nuclear magnetic resonance (NMR) has also seen a number of advances in the past years, including magnetic and pole improvement assignment (Zheng *et al.*, 2003; Oezguen *et al.*, 2002).

Structure based drug design is most powerful when it is part of an entire drug lead discovery. A review by Antil (Bailey-Kellogg *et al.*, 2000), states that the combination of combinational chemistry and structure based design can lead to the parallel synthesis of focused compound libraries. It is important to consider that structure – based drug design directs the discovery of a drug lead which is not a drug product but, specifically, a compound with at least micromolar affinity for a target (Pervushin *et al.*, 1997). The time devoted to the structure based drug design process, as in this review may represent only a fraction of the total time towards developing a marketable drug product. This review is intended to provide an overview of the process, of structure – based drug design from the selection of a target to the generation and evaluation of lead compounds.

Overview of the process

The process of structure – based drug design is an interative one and often proceeds through multiple cycles beside an optimized lead goes into phase I clinical trials Fig. 1). The first cycle include the cloning, purification and structure determination of the target protein or nucleic acid by one of the three principal methods: X-ray crystallography, NMR, or homology modeling, using computer algorithm, compounds or fragments of compounds from a data – base are positioned into a selected region of the structure. These compounds are scored or ranked based on their steric and electrostatic interactions with the target site and the best compounds are tested with biochemical assays. In the second cycle, structure determination of the target in complex with a promising lead from the first cycle, one with at least micro-molar inhibition in vitro, reveals sites on the compounds that can be optimized to increase potency. Additional cycle includes synthesis of the optimized lead structure determination of the new target: lead complex, and further optimization of the lead compound. After several cycle of the drug design process, the optimized compounds usually show marked improvement on binding and often, specificity for the target.

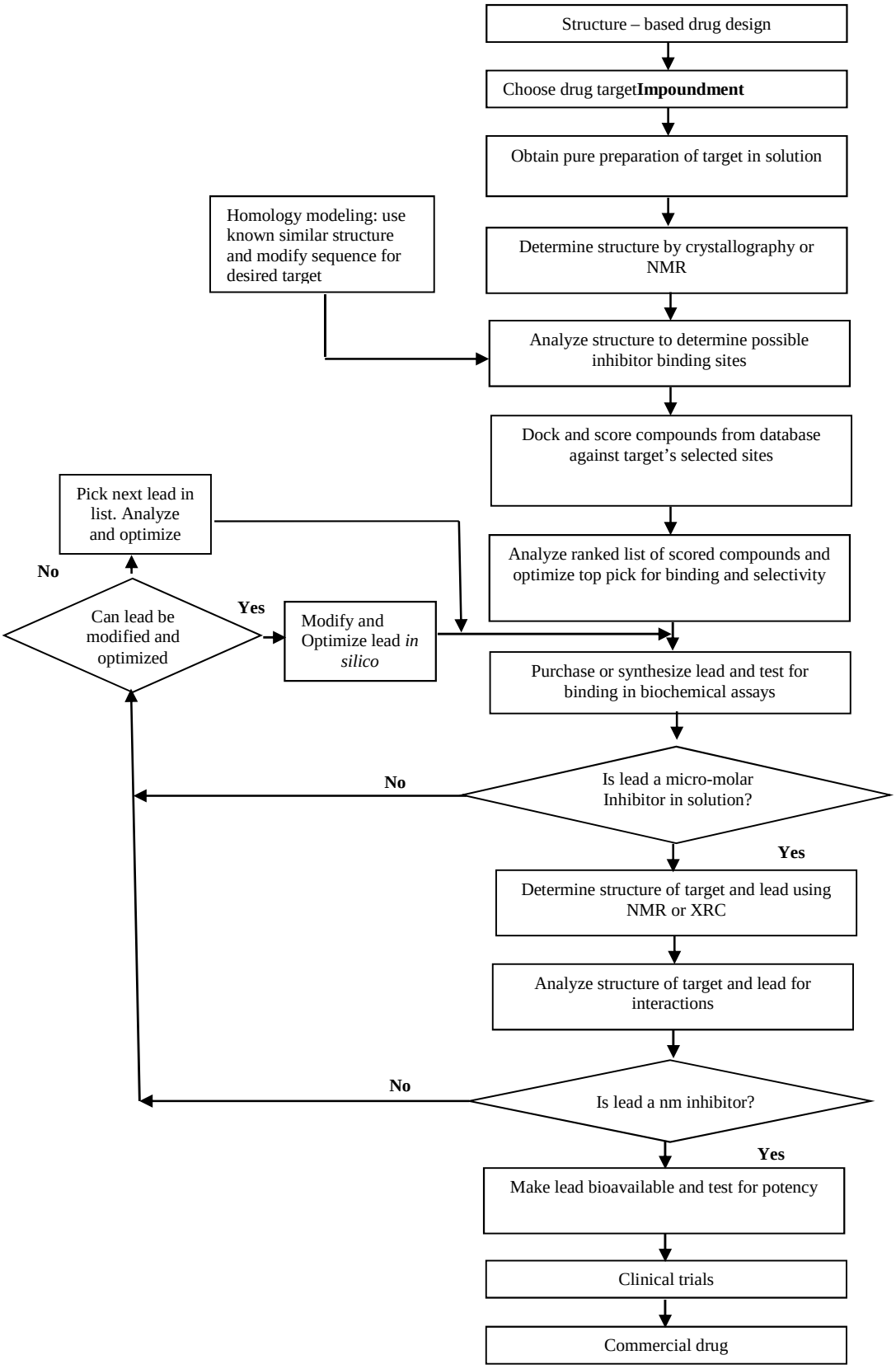

Fig 1: The process of structure- based drug design

Choice of a drug target

The choice of a drug target is primarily made on a biological and biochemical basis. The ideal target macro-molecule for structure – based drug design is one that is closely linked to human disease and binds a small molecule in order to carry out a function. The target molecule usually has a well defined binding pocket. Many good drug targets are protein; however, drug design against RNA targets with well defined secondary structure, like the bacterial ribosome and portions of HIV genome, has also been effective, Recent reviews highlights some of the RNA structure – based projects underway (Pervushin *et al.,* 1997; Antel, 1999). In diseases caused by the malfunction of human proteins small drugs against G protein coupled receptors (GPCRS) represent at least 25% of currently marketed drugs (Verlinde, 1994). Small molecules that modulated the function of ion channels, proteases, kinases and nuclear hormone receptors make up another 22% of the market.

The goal in developing drugs against pathogenic organisms is total inhibition leading to the death of the pathogen; so the target should be crucial in that it is part of a crucial cycle in the cell

Antimicrobial drug targets should be essential, have a unique function in the pathogen, be present only in the pathogen, and be able to be inhibited by a small molecular.

Cancer targets can be difficult because targets are often somatic cell mutants of protein that regulates essential cellular functions resulting in the loss of a function, of course, it is difficult for a small molecule to potentiate the recovery function. However as pointed out in a perspective by Kaelin (Gallego, 2001) a loss of function in one molecule is often correlated with a gain of protein in another.

Evaluating structure for structure – based drug design

Once a target has been identified, it is necessary to obtain accurate structural information. There are three primary methods for structure determination that are useful for drug design;

- X – ray crystallography
- NMR
- Homology modeling

The key steps in structural – based drug design include

1) Preparation of the target protein and compound library for docking
2) Determining a favorable binding pose for each compound
3) Rating the docked structures.

Molecular docking is a structural based computer simulation procedure that products the orientations or conformation of a receptor – ligand complex and use this knowledge to predict the binding affinity between the molecules in the complex (Afshar, 1999). Molecular docking is the main fool for Virtual Screening. This technique was pioneered in early 1960's and remains the generally acceptable method in drug discovery. Molecular docking involves two component search algorithm and scoring functions (Hopkins *et al.,* 2002) search algorithm predicts the conformation or orientation (posed) of a ligand in the target binding site while scoring functions predicts the binding affinity between the ligand and target protein (Kaelin, 1999).

Examples of structure-based design leading to approved drugs

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. 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.

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 myelogenousleukemia 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

Additional examples include:

Many of the atypical antipsychotics,Cimetidine, the prototypical H_2-recptor antagonist from which the later members of the class were developed, Selective COX-2 inhibitor NSAIDs, Enfuvirtide, a peptide HIV entry inhibitor, Nonbenzodiazepines like zolpidem and zopiclone, Raltegravir, an HIV integrase inhibitor, SSRIs (selective serotonin reuptake inhibitors), a class of antidepressants, Zanamivir, an antiviral drug.

The ligand-based drug discovery

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. 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.

This approach involves the analysis of ligands known to interact with a target of interest. The Overall goal is to represent compounds in such a way that the physicochemical properties most needed for their desired interactions are retained, whereas unnecessary information not relevant to the interactions is discarded. It is considered an indirect approach to drug discovery in that it does not necessitate knowledge of the structure of the target of interest (Tegar *et al.,* 2013). The ligand based design exploits the knowledge of known active and inactive molecules for chemical similarity search or QSAR. This design is ideal where the 3D structures of the target proteins are not available (Mahajan *et al.,* 2006).

There are two central approaches:

Selection of compounds based on chemical similarity to knownactive compound using similarity search. This has to do with searching for chemicals that are similar to the active compound or the drug that is being studied for modifications; and The construction of a QSAR model that predicts biologic activity from chemical structure. Ligand-based rely on the Similar Property Principle, published by Maggiora (Tegar, M. and H. Purnomo (2013), which states

that molecules that are structurally similar are likely to have similar properties. Molecular descriptors employ in this approach includes molecular weight, surface areas, ring content, rotatable bonds, interatomic distances, bond distances, atom types, planar and non-planar systems, molecular walk counts, electronegativities, polarizabilities, symmetry, atom distribution, topological charge indices, functional group composition, aromaticity indices, solvation properties, and manyothers.

***Quantitative-structure activity relationship (QSAR)*:**
This is a computational approach that is designed to find the relationship between chemical structures, physicochemical properties and biological activities of compounds (Shoichet, B. K. et al 1992. QSAR models are mathematical models that relate the structurally related property to another property or activity of interest (Marshall, 1987). The three components of the model are:
A data set that provide activity (usually experimentally measured) for a group of chemicals. This has to do with actions of a set of compounds determine experimentally that are closely related when applied to a particular ligand.
A structural and structure related data base for the same group of chemicals. This is data of related structures and a means of relating (usually a statistical analysis method) these two data arrays. This method ranged from simple linear regression to a more complex neural network (Kapetanovic, 2008). The common QSAR software is ADMET predictor.

Pharmacophore mapping
In 1998, the International Union of Pure and Applied Chemistry formally defined a pharmacophore as 3Dspatial arrangement or the electronic feature that is necessary for optimal molecular interactions with specific biological targets and to elicit its biological response (Guner and Bowen, 2014). A Pharmacophore is an abstract concept, it represent the chemical feature that makes the ligand be complementary to the receptor in the 3D dimensional space (Kapetanovic, 2008). A pharmacophore can be designed based on complementarity to a known ligand binding site (Kapetanovic, 2008). Therefore, an effective pharmacophore will contain information about functional groups that interact with the target, as well as information regarding the type of non-covalent interactions and interatomic distances between these functional groups/interactions.
This arrangement can be derived either in a structure-based manner by mapping the sites of contact between a ligand and binding site or in a ligand-based approach. The former can be achieved by analyzing one or several co-crystal structures attached to the target protein (Kurogi, and Guner, 2001). The most common software packages used for ligand-based pharmacophore software's include Catalyst, Ligand Scout , DISCO, and GASP (45).These packages use different molecular approaches to identify common chemical features arranged in certain positions in three-dimensional space. These chemical features include hydrophobic regions, hydrogen-bond donors, hydrogen-bond acceptors, positive ionizable, and negatively ionizable regions (Kapetanovic 2008).

Conclusion
CADD is now widely recognized as a viable alternative and complement to highthroughput screening. The search for new molecular entities has led to the construction of high quality datasets and design libraries that may be optimized for molecular diversity or similarity. Conversely, advances in molecular docking algorithms, combined with improvements in computational infrastructure, are enabling rapid improvement in screening throughput. Propelled by increasingly powerful technology, distributed computing is gaining popularity for large-scale screening initiatives. Combined with concerted efforts towards the design of more detailed physical models such as solubility and protein solvation, these advancements will, for the first time, allow the realization of the full potential of lead discovery by design.

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FUW Trends in Science & Technology Journal ftstjournal@gmail.com
April, 2016 Vol. 1 No. 1 – e-ISSN: 24085162; p-ISSN: 20485170 pp 158-164