

Chapter 2

Discovery: Use of Systems Biology for Identifying Targets

In our introduction, we emphasized that a combination of reductionist (mechanism-based) and holistic (hypothesis-based) tools in the drug screening process may increase the efficiency of overall Drug Discovery. Among notable holistic tools are screens that target discovery and characterization of molecular probes (compounds) that will enable the investigation of fundamental biological function at molecular, cellular and whole organism levels. Such screening usually occurs at the earlier stages of drug discovery. However, sometimes the required biological insights and understanding of both the normal physiology and the aetiology of the disease process are too sparse to allow for an appropriate screening effort. In those instances, exploratory experiments and ad hoc assay designs are required to test and refine particular hypotheses regarding potential target viability. To that end we discuss other holistic tools aimed at characterizing biological dynamics at the biochemical and molecular biology levels in [Chaps. 3](#) and [4](#).

An analysis of the druggable space suggests that pharma is reaching a saturation point in terms of available targets, and mechanism-based screens may not represent an optimal strategy for targeting this very narrow point within the druggable space. One hole in this technological strategy is that it avoids cross fertilization between disease-modifying genes and the druggable genome [[1](#)]. Additionally, drug pleiotropy ([Chap. 4](#)) may cause undesirable off-target effects. A rationale for selecting drug combinations by systems tools is proposed in [Chap. 3](#).

Combinatorial chemistry tools help to rationalize the DD process by exploiting several chemical and informational tools (none of them being relevant to a systems approach described in this report, however). The Achilles heel of the present approach is a strong emphasis on high-affinity ligands (low affinity ligands are important for cell-cell interactions and the immune system) and the failure to detect molecules that bind covalently to the receptor.

Qualitative and quantitative screens and other filters only facilitate the identification of lead substances (i.e., those compounds that will lend themselves to optimization by classical medicinal chemistry efforts). Since every hit will not

necessarily translate into a marketable product, the aim of this stage of the search is to seek a facility that will eventually enable virtual chemistry screening.

Definitions:

- **Top-down** is a reductionist approach analyzing a system down to the mechanistic level.
- **Bottom-up** is a holistic approach, seeking to cross boundaries and hierarchic organization to synthesize the knowledge to the cell, organ and organismic levels. This is a novel approach, building up from mechanistic knowledge.
- **Druggable** genome represents a part of the genome which could potentially be accessed by an effective drug candidate. It represents amenability to modulation of a target by drugs.
- **MoA** (Mechanism of Action) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect.
- **SAR (QSAR)** is the process by which chemical structure is (quantitatively) correlated with a well defined process, such as biological activity or chemical reactivity.

This part encompasses a short introduction to [Chaps. 2 and 3](#), and covers target-based and physiology-based approaches as well as combined systems approaches. In a target or mechanism-based (top-down, or so-called reductionist) approach, scientists first identify a protein or molecular mechanism relevant to a disease process and then use screening to find compounds that interact with or modulate it. The present effort may have swung too far in the direction of the reductionism implicit in target and mechanism-based drug discovery.

Bottom-up (holistic) methods of identifying interesting targets and the compounds that interact with them, often result in compounds that, in animal systems or in humans, show that the underlying mechanism is more complicated than was previously thought. This is an argument for less reductionism. On the other hand, earlier, a lot of DD was driven by phenotypic screening, in which compounds were tested for a desired readout in cell or animal systems and their target and mechanism were typically unknown at first. This is called a phenotypic cell and organism-based (holistic) approach.

The mechanism-based approach is unlikely to be abandoned anytime soon, but some people believe that the traditional cell- and organism-based strategy (also called the physiological strategy) should not have been discarded completely and should now be given renewed emphasis. *The combined reductionism and holistic approach is most germane to the systems approach*, utilizing both directions in the feedback loops [2].

2.1 Identifying Targets and Druggability Space

Since the early 1990s, the target-based drug discovery paradigm has been the dominant approach in the pharma industry. It takes a rational approach by defining the specific molecular mechanism or Mechanism of action (MoA) to be targeted by the treatment from biological and clinical findings. However, it does not translate

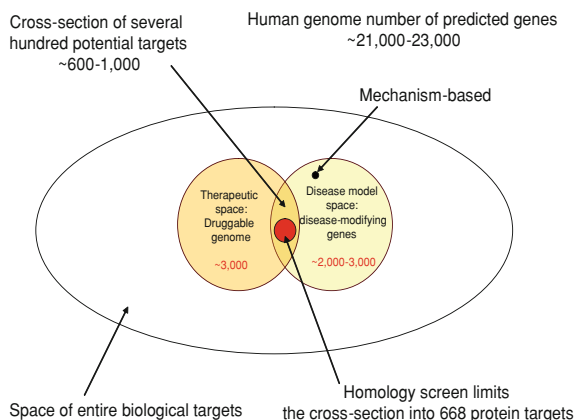


Fig. 2.1 Number of drug targets depicted in Venn diagram The effective number of possible targets can be determined by a homology subset of the intersection of the number of disease-modifying genes and the druggable subset of the human genome [4, 5]. A cross-section between druggable and disease-modifying space represents the most promising targets for DD. Of those, Bakheet and Doig identified 668 proteins as a narrow target, based on a vector machine homology screen

into a high success rate for novel targets, presumably because our level of insight into disease dynamics and their associated biological processes is not sufficient to predict the therapeutic value and druggability of a novel target. Figure 2.1 shows a logical Venn diagram depicting how targets can be classified and/or eliminated from a potential search. Note, the Bakheet and Doig estimate may look very pessimistic. However, targeting proteins is likely a better approach since nearly all drugs act at the protein level (except transcription process inhibitors). Fortunately, the proteome is a much better target than the genome, owing to alternative splicing and post-translational modifications. Mechanism-based approaches select a single known mechanism and are represented by a single Point; it limits the effort to an unreasonably small sampling of target space. Physiology-based and function-based approaches do not employ any assumption regarding the MoA and operate within their respective disease-modifying spaces. Disease-modifying genes are those involved in disease onset or progression. More on global mapping of pharma space is in Paolini et al. [3].

The characteristics of druggable compounds should be such that they can be delivered effectively to the target tissues and cells [6]. These authors estimated that the upper limit of molecular targets in the human genome that represent an opportunity for further therapeutic treatment is approximately 6,300 human proteins that are similar to sequences of known protein targets collected from the DrugBank database (about 20% of human proteome). On the other hand, Drews [7, 8] identified about 5,000–10,000 potential targets on the basis of number of disease-related genes. Theoretical prediction of protein function from the gene sequence computationally remains an excruciatingly imprecise science. Despite these hurdles, CuraGen's Golden (in 2002) was in no doubt that deciphering the druggable genome sequence will ultimately restock the therapeutic pipeline.

It is clear from the distribution of the gene-family populations that there are no undiscovered large protein families, which indicates that remaining targets will be members of very small families. Clearly, the number of potential protein targets could be larger than the number of genes, owing to post-translational modifications and the assembly of functional complexes; however, this is not likely to increase the number of specific drug-binding sites.

Furthermore, the question then becomes which specific target will be *druggable and disease-modifying*. It is estimated that about 10% of the entire human genome is involved in disease onset or progression, resulting only in approximately 3000 potential targets suitable for therapeutic intervention. The key is to discriminate between the disease-associated versus disease-modifying genes. Hajduk et al. [9] suggested a way to employ Systems Biology to identify potential disease targets.

All drugs somehow interfere with signal transduction, receptor signaling and biochemical equilibrium. Additionally, for many drugs we know, and for most we suspect, that they interact with more than one target (pleiotropy). So, there will be simultaneous changes in several biochemical signals, and there will be feedback reactions from the perturbed pathways. In most cases, the *net result will not be linearly deductible from single effects and SB tools must be applied*. In addition, this phenomenon is a source of off-target effects.

For drug combinations, this is even more complicated. Thus, a clinically relevant ‘target’ might consist not of a single biochemical entity, but of simultaneous interference of a number of receptors (pathways, enzymes and so on). And, only the net clinical effect will be beneficial. Such target definition, not derived from a single direct chemical interaction *will require input from systems biology* [10]. Clinical input is crucial: the ability of a protein to bind a small molecule with the appropriate chemical properties at the required binding affinity might make it druggable, but does not necessarily make it a potential drug target, for that honor belongs only to proteins that are also linked to disease.

The results of screening in the pharmaceutical industry and the limited number of druggable targets suggest that, within the next decade, the industry could reach a position in which ‘hits’ or chemical leads are available for most potentially druggable targets. The challenge for the industry will then not necessarily be in the discovery of leads, but in *discovering and assessing the therapeutic utility of its leads and druggable targets (indications)* [11]. Furthermore, filtering of targets will become imperative as the space for potentially biologically relevant pharmacophores is enormous, and even large libraries populate it only sparsely, and attrition remains severe.

2.1.1 Bioinformatics Inputs (BI Inputs)

Drug-likeness and the Ro5 (see below) has been used to advantage, but as our knowledge of SB grows there is a need to move towards more predictive approaches. This will require prediction of where and how drugs interact with

metabolism, which can be addressed by cheminformatics methods to assess molecular similarity between a putative drug and reactive metabolites. Concluding, the inputs of SB at identifying drug targets and BI are clearly needed in order to arrive at a target identification and validation.

2.2 Combinatorial Chemistry Tools

Combinatorial Chemistry methods facilitate:

- The synthesis of large libraries of small organic compounds and peptides
- The evaluation of these libraries against molecular and cellular targets
- The computer simulation of a large number of different but structurally related molecules

Combinatorial chemistry has contributed significantly towards the evolution of the DD process with the major emphasis in the field evolving towards methods to accelerate lead generation/lead optimization, focused parallel synthesis, high throughput technology, and chemical biology. It is justified on the assumption that the estimated size of the synthetically tractable space is in the order of 10^{20} – 10^{24} molecules [12].

The latest report from a series of combinatorial chemistry surveys is available [13], providing bioactive libraries of different types. A new grouping highlights discovery and characterization of *molecular probes* or tool compounds allowing an *investigation of fundamental biological function at molecular, cellular and whole organism levels*. Such probes may be defined as small molecules that elicit a cellular event or phenotypical result through the specific interaction with a target protein, pathway or analyte. A good example is a breast cancer cell migration probe [14].

2.2.1 BI Inputs

Various computational tools are available as decision support tools for medicinal chemists involved in compound library synthesis programs [15]. These methods can be used to assemble a flexible library consisting of a structure-based library design followed by property-biased library refinement and final selection according to structure-activity-relationship considerations. Parallel Computing has facilitated the development of structure-based tools that are able to screen hundreds of thousands of molecules [16].

Further lead improvement is achieved with the help of diversity-oriented syntheses and asymmetric (chiral) compound preparation methods (see below).

2.2.2 Diversity Tools

Diversity can be accomplished chemically and biologically while seeking tools which can enrich the chemical space. Although purely chemically-based, diversity tools will have reached their full potential once the **SB and BI tools** are applied (as to any other OMICs) and explored.

2.2.2.1 Diversity-Oriented Synthesis and Discovery

Diversity-Oriented Synthesis (DOS) aims to prepare (mostly via solid-phase chemistry) collections of structurally complex and diverse compounds from simple starting materials, typically from ‘split-pool’ combinatorial chemistry. The DOS concept is typically applied through four elements of diversity:

- Building block
- Functional groups
- Stereochemistry, and
- Skeleton branching

Mimicking the broad structural features of natural products may allow the discovery of compounds that modulate the functions of macromolecules for which ligands are not known [17].

A simpler synthetic planning strategy is also available. In it a “retrosynthetic analysis” of the desired target structure is employed (which means a step-wise analysis of chemical transformations, starting from the complex target structure towards more simple starting materials) [18].

2.2.2.2 Differentially Expressed Proteins

DNA microarrays have allowed researchers a tool to detect differential expression of numerous genes in a small sample and have clearly revolutionized the way gene expression analysis is now carried out (differentially expressed protein screen; detected against a normal background). These microarrays are, however, confined to the detection of gene transcripts and do not permit the analysis of the translational product (protein). The recent development of protein microarrays now offers the ability to simultaneously analyze the protein expression of several hundred proteins to measure the presence, biochemical characteristics and activation state of a considerable number of proteins in a single experiment.

2.2.2.3 Phage Display

Phage display (phage display screen) provides another diversity tool, based on the exploration of the most natural and efficient DD process. Molecular imaging is at the forefront in the advancement of in vivo diagnosis and monitoring of disease.

New peptide-based molecular probes to facilitate disease/cancer detection are rapidly evolving. Peptide-based molecular probes that target apoptosis, angiogenesis, cell signaling and cell adhesion events are in place. Phage display technology is commonly employed to identify peptides as tumor-targeting molecules. Numerous peptides that bind cancer cells and cancer-associated antigens have been reported from phage library selections.

Phage display screens have also been performed in live animals to obtain peptides with optimal stability and targeting properties *in vivo*. To this point, few *in vitro*, *in situ*, or *in vivo* selected peptides have shown success in the molecular imaging of cancer, the notable exception being vascular targeting peptides identified via *in vivo* selections. However, determining which peptide best translates into a useful drug is of particular importance. Examination of successfully marketed drugs has highlighted key features of a winning agent, including low molecular weight, high affinity, stability, solubility; lipophilicity and conformational rigidity (see Ro5).

A number of other platform strategies have been developed to screen polypeptide libraries for ligands targeting receptors selectively expressed in the context of various cell surface proteomes (cell display, ribosomal display, mRNA display and covalent DNA display) while phage display being by far the most utilized.

2.2.2.4 Chirality Tools

Advantages of using stereochemically pure drugs are that:

- Total dose could be reduced,
- The dose–response relationship would be simpler,
- A source of variability would be removed, and
- Toxicity from the inactive stereoisomer would be minimized.

Stereospecific interactions at recognition sites result in differences in both biological and toxicological effects. This fact underlies the continuing growth in chiral chemistry, rooted as it is in fundamental biochemistry.

The pharmaceutical industry has undergone a strategic shift and embraced the wide spectrum of asymmetrical synthetic methods, leading to chiral compounds, now available [19]. The use of these processes in developmental synthesis and large-scale manufacturing has provided new challenges in DD, motivated by a desire to improve industrial efficacy and decrease the time from the conception of a new drug to the market.

Chiral compounds are typically synthesized by asymmetrical synthesis [20], using a rapid screening method for monitoring specificity using both combinatorial chemistry and mass spectrometry.

BI Inputs: Few quantitative features are included in the chirality screen. Hologram quantitative structure-activity relationships (HQSAR) may be performed on a set of structurally diverse molecules with known human oral bioavailability.

The HQSAR model is useful for the design of new drug candidates with increased bioavailability as well as in the process of chemical library design, virtual screening, and HT screening [21].

2.2.2.5 Homology Tools at Discovery

Similarity metrics (homology modeling), and chemoinformatics are tools which further reduce the number of hits. They all employ some degree of quantitative data handling. Homology tools represent purely **BI input**.

Homology modeling (comparative modeling), refers to constructing an atomic-resolution model of the “target” protein and an experimental 3D structure of a related homologous protein (the “template”). To cite the author—“homology modeling relies on the identification of one or more known protein structures likely to resemble the structure of the query sequence, and on the production of an alignment that maps residues in the query sequence to residues in the template sequence. The sequence alignment and template structure are then used to produce a structural model of the target. Because protein structures are more conserved than DNA sequences, detectable levels of sequence similarity usually imply significant structural similarity” [22].

2.2.2.6 Cheminformatics

Cheminformatics combines chemistry and computer science (e.g., chemical graph theory) and mining the chemical space. Several selected tools are reviewed below:

- A data mining approach has been developed in order to construct a structure-diverse sub-library from the large PubChem (<http://pubchem.ncbi.nlm.nih.gov/>) database [23], suitable *in silico* virtual screening and in vitro HTS drug screening.
- Immunoinformatics, represents an emergent sub-discipline of BI, proposed to develop computational vaccinology as a potent tool in the quest for new vaccines.
- A text-based search engine allows efficient searching of compounds (in ChemDB; <http://www.chemdb.com>; containing nearly 5 million commercially available small molecules) based on over 65 million annotations from over 150 vendors [24].

2.2.2.7 Fragment Based DD

Fragment Based DD (FBDD) has developed over the last decade to take its place as a standard tool in the pharma industry [25]. It has yielded numerous, well-documented successes, and has proved to be the tool of choice for targets where much structural information is forthcoming, and which possess a well-defined,

reasonably-small binding site [26]. To enable screening, a useful parameter has been introduced, the ligand efficiency, which is defined as the free energy of binding divided by the non-hydrogen atom count [27]. Further improvement follows, through so-called ‘fragment evolution’ and ‘fragment linking’.

The next few years should see a maturing of the area, and as our understanding of how the concepts can be best applied increases. Undoubtedly, **BI input** will be introduced here in order to optimize the fragment chemistry.

2.2.3 Qualitative and Quantitative Screens and Filters

Several exclusionary filters have been devised to reduce the number of hits to manageable levels with the aim of identifying a lead substance. Rule of Five (Ro5) and extensions represent one such tool. Some screens have been devised that remove reactive chemical functionalities, on the premise that compounds having covalent chemistry capabilities have no place in DD (a simple qualitative rule or rule of thumb). The original Ro5 (Lipinski rule) deals with orally (lipidic) active compounds and defines the following simple physicochemical parameter ranges:

- $\log P \leq 5$
- H-bond donors ≤ 5
- H-bond acceptors ≤ 10 ,

These physicochemical properties are typically associated with 90% of orally active drugs that have achieved phase II clinical status. Essentially they are associated with acceptable aqueous solubility and intestinal permeability and comprise the first steps in oral bioavailability. This concept has been extended to include drug-like physicochemical properties [28]. Lead-like drugs refer to the screening of small MW libraries with detection of weak affinities in the high micromolar to millimolar range. A rule of three (Ro3) has been coined for these small molecule fragment screening libraries.

Simple kinetics (binding kinetics) in post Ro5 optimization/screen parameters in lead discovery and optimization is discussed below. Current lead discovery is mainly focused on identification of novel active and selective agonists, antagonists, or inhibitors that provide viable starting points into subsequent lead finding and optimization campaigns. The determination of binding kinetic profiles for efficacy and selectivity assessment in the context of lead discovery is widely under-appreciated, even though increasing evidence exists that renders *compounds that exhibit long binary complex residence time (in blood) better lead candidates* (Chap. 7). This behavior will highlight the underlying enzymological principles of so-called slow k (off) compounds (very low dissociation constant from the complex) and will provide examples that demonstrate that efficacious compounds display a distinct kinetic signature and

will introduce a fragment-based lead discovery concept that guides medicinal chemistry towards long residence time kinase inhibitors for next-generation drugs.

2.2.3.1 BI Inputs

The use of computational rules as filters is an evolving field. A paradigm shift in drug discovery has resulted in the integration of Pharmacokinetics (PK) and DDv activities into the early stages of lead discovery [29]. In particular, *in silico* filters are used to help identify and screen out compounds that are unlikely to become drugs. Recent computational approaches towards the design of drug-like compound libraries, the prediction of drug-likeness, as well as intestinal absorption through passive transport, and the permeation of the blood-brain barrier serve as examples. The PK properties should also be included as important filters in virtual screening. Current development in theoretical models allows prediction of drug absorption-related properties, such as intestinal absorption, and blood-brain partitioning [30]. Both, chemical and computational methods serve as standard filter tools in the pharmaceutical industry.

2.2.4 Structure-Activity Methods (SAR/QSAR)

Quantitative structure-activity relationship (QSAR) is the process by which a chemical structure (a possible future pharmaceutical) is quantitatively correlated with a well defined process, such as biological activity or chemical reactivity (this effort has substantial **BI and SB inputs**). Biological activity can be expressed quantitatively as a concentration of a substance required to cause a certain biological response (this is just one aspect of the pure pharmacology, only half of the story; the key to characterization is equally functional impact). When physicochemical properties or structures are expressed by numbers, a mathematical relationship or quantitative structure-activity relationship, between the two can be established. The biological activity is usually measured in assays to determine the level of inhibition of particular signal transduction or metabolic pathways.

Unger and Hansch defined good practice in QSAR [31]:

- Select independent variables
- Justify the choice of the variables by statistical procedures,
- Apply the principle of parsimony,
- Have a large number of objects compared to the number of variables,
- Try to find a qualitative model of physicochemical or biochemical significance (chemical descriptors).

At present, more subtle quantitative methods are available:

- Chemical Computing Group Inc. developed novel 3D-QSAR descriptors allowing the 3D properties of compounds to be incorporated into traditional QSAR models, including Probabilistic Receptor Potentials to calculate the substrate's atomic preferences in the active site [32].
- Newer QSAR approaches [33]. The method seeks to characterize molecules by means of mathematical approaches used to establish a correlation between descriptor values and biological activity.
- New mathematical tools of Multivariate analysis include Artificial Neural Networks, Regression Trees, Random Forests, MARS (splines) and other methods (statistical). Various molecular descriptors have been used.
- The newest developments involve descriptors of 3D/4D QSAR, allowing for complex conformational methodology, covering a classification of drugs by their activity, MoA, target and binding site [34].

2.3 Summarizing

- This chapter discusses a mix of mostly reductionistic, qualitative and quantitative tools, at the chemistry discovery level.
- Chemical and other screening methods are a must because a typical compound entering a Phase I clinical trial undergoes years of rigorous preclinical testing but still only has about 8% chance to reach the market.
- The number of druggable targets (number of specific drug-binding sites) is becoming exhausted and saturated by discovered drugs.
- The present insight into disease and biological processes is not sufficient to predict the therapeutic value of druggability of a novel target.
- While assessing the lead utility, the key is discrimination between disease-associated versus disease-modifying genes.
- Despite the initial promise of combinatorial chemistry, particularly large library combinatorial chemistry, to greatly accelerate drug discovery, this approach has not been fully effective as a means to build the compound collections of pharmaceutical and biotechnology companies.
- Combinatorial chemistry, though, has already had a great impact on DD programs and has contributed to the discovery of drugs that are currently in clinical trials or already in the market. Its significance will grow.
- Further lead improvement/screen can be achieved with the help of diversity-oriented syntheses and chiral compound preparation methods. Computer-based guidance will help.
- Several chemical BP tools are available to guide similarity searches.

- Application of qualitative rules such as rule-of-thumb (ROT) and computational filters will become more efficient. The huge number of active motifs can be reduced to a handful of promising lead series.
- QSAR is a well established tool where physicochemical and molecular descriptors are correlated with bioassay outputs.
- *In silico* tools will need to become a part of every pharmacologist's tool kit and this will require training in modeling and informatics, alongside in vivo, in vitro and molecular skills.
- A suite of QSAR models for making quantitative prediction of interactions of a test molecule with important classes of human proteins should be integrated into the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) modeling effort (see [Chap. 7](#)).

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