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Drug Discovery

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Abstract

The drug industry is one of the major players guiding the development of the medicines, biotechnology & pharmacology field. Drug discovery is the process by which drugs are discovered and designed. It is a process which aims at identifying a compound therapeutically useful in curing & treating disease. The process of drug discovery involves the identification of candidates, synthesis, characterization, screening & assays for therapeutic efficacy. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials. Developing a new drug is a tedious & expensive undertaking, despite promising discoveries and multibillion dollar investments for new drug development is quietly undergoing crisis. Currently, all existing therapies together hit only about 400 different drug targets. It is estimated that there are at least 10 times as many potential drug targets that could be exploited for future drug therapy.

Keywords: Drug discovery; Drug development; Clinical trials; Potential drug targets; Clinical trial

Introduction

Drug discovery is a process, which aims at identifying a compound therapeutically useful in treating and curing a disease. Typically a drug discovery effort addresses a biological target that has been shown to play a role in the development of the disease or starts from a molecule with interesting biological activities.

The process of drug discovery involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials. Drug discovery and development is an expensive process due to the high costs of R&D and human clinical tests. The average total cost per drug development varies from US$ 897 million to US$ 1.9 billion. The typical development time is 10-15 years. The developing world suffers the major burden of infectious disease, yet the range of drugs available for the treatment of many infectious diseases is limited. In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery [1]. At present a new approach is being tried to understand how disease and infection are controlled at the molecular and physiological level and to target specific entities based on this knowledge.

Steps in Modern Drug Discovery

Step 1: Target identification

Target identification is the first key stage in the drug discovery pipeline. Generally speaking, a drug target is the specific binding site of a drug *in vivo* through which the drug exerts its action [2]. A specific drug target might have the following characteristics:

1. The drug target is a biomolecule(s), normally a protein that could exist in isolated or complex modality.
2. The biomolecules have special sites that match other.
3. The biomolecular structure might change when the biomolecule binds to small molecules and the changes in structure normally are reversible.
4. Following the change in the biomolecule's structure various physiological responses occur and induce regulation of the cell, organ, tissue, or body status.
5. The physiological responses triggered by the changes in biomolecule structure play a major role in complex regulation and have a therapeutic effect on pathological conditions.
6. The expression, activity, and structure of the biomolecule might change over the duration of the pathological process.
7. Small molecules binding to the biomolecules are drugs.

Figure1: Drug Discovery Pipeline.

As is apparent from the above discussion, a drug target is a key molecule involved in a particular metabolic or signal transduction pathway that is specific to a disease condition or a specific disease. However, the term 'drug target' itself has several limitations and is debated within the pharmaceutical industry. In this respect, several points should be kept in mind.

First, a drug target is a relative concept. For starters, a drug target is, just like other biomolecules, also a biomolecule involved in a transduction pathway. The difference between the two is only in their location and role in the transduction pathway. Another aspect is that a drug target is disease-dependent, that is, every target is involved in a special spectrum of diseases.

Second, most human diseases are rather complicated and involve many risk factors, so there are clearly many different drug targets with respect to a specific disease.

Targeting a specific target could not conceivably cure a kind of disease. However, the involvement of many targets in a disease does not mean that each target shares equally in the pathogenesis of the

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disease and thus drugs targeting these targets would not be equally effective in the therapy of the disease.

Third, drug targets can change, which means that with the development of insights into biomolecules and their role in the pathogenesis of a certain disease, drug

targets might be not as important as or may be much more important than currently believed. In fact, the establishment of drug targets is based on understanding of the pathogenesis of the disease.

Fourth, there are many drugs targeting the same target and one drug may have more than one target. The relationship between a drug and its target is not one-to- one but one-to-many or many-to-one.

Fifth, when a new drug target is discovered and validated, researchers usually hope to obtain more specific drugs targeting the target. However, a key understanding to keep in mind is that the body is a subtle organism and a more specific drug might disrupt the homeostasis of the body. Compared to aspirin, rofecoxib is a specific COX-2 inhibitor.

However, studies had shown that rofecoxib increases cardiovascular risks, resulting in rofecoxib's withdrawal from the drug market.

Sixth, a drug target usually refers to a single biomolecule.

According to whether there are drugs available, a drug target can be classified into two classes: established drug targets and potential drug targets. The former are

those for which there is a good scientific understanding, supported by a lengthy publication history regarding both how the target functions in normal physiology and

how it is involved in human pathology. Furthermore, there are many drugs targeting this target. The latter are those biomolecules whose functions are not fully

understood and which lack drugs targeting them. Potential targets suggest directions for completely new drug research.

Step 2: Target validation

New target validation is the basis of completely new drug exploration and the initial step of drug discovery.

New drug target validation might be of great help not only to new drug research and development but also provide more insight into the pathogenesis of target related diseases [3]. Basically, the target validation process might include six steps:

1. Discovering a biomolecule of interest.

Figure 2: Bioassay of lead molecule with target.

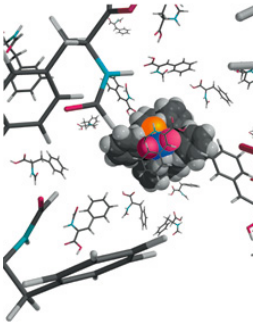

Figure 3: Lead molecule.

2. Evaluating its potential as a target.
3. Designing a bioassay to measure biological activity.
4. Constructing a high-throughput screen.
5. Performing screening to find hits.
6. Evaluating the hits.

The drug discovery process starts with the identification or growing evidence of, biological targets that are believed to be connected to a particular condition or pathology. Information supporting the role of these targets in disease modulation can come from a variety of sources [4]. Traditionally, the targets have been researched and largely discovered in academic laboratories, and to a lesser extent in the laboratories of pharmaceutical and biotechnology companies. Basic research into understanding the fundamental, essential processes for signaling within and between cells and their perturbation in conditions has been the basic approach for establishing potential targets suitable for drug intervention.

Step 3: Lead discovery

Once a disease- associated molecular target has been identified and validated in disease models, in the lead generation phase, compounds are identified which interact intact animals or disease-related cell-based models that can provide information about the integrative response of an organism to a pharmacological intervention and hereby help to predict the possible profile of new drugs in patients. This is accomplished primarily with knock-out or knock-in animal models; small molecule molecular target *in vitro* usually precedes the validation of the therapeutic concept *in vivo*; together this defines its clinical potential. Validation involves studies in molecular target *in vitro* usually proceeds with the target protein and modulate its activity. Libraries of compounds that are either synthetic chemicals, peptides, natural or engineered proteins, or antibodies are exposed to the target in a manner that will detect and isolate those members of the library that interact with and, preferably, have an effect on the target [5-8]. The compounds selected are called "leads". Initially screening can be performed by searching for compounds that bind to the target, but binding is not sufficient for therapeutic activity. More recent screening procedures include an activity-based readout as part of the initial screening assay. For example, if the goal is to inhibit a protein that is involved in activating the expression of a particular gene or set of genes, the assay can include readout to determine if the expression of the gene is reduced by the compound. Such assays can be cell-based, but more often they are enzymatic assays that can be performed in a high-throughput manner for compounds that bind to the target, but binding is not sufficient for therapeutic

activity. More recent screening procedures include an activity-based readout as part of the initial screening assay. For example, if the goal is to inhibit a protein that is involved in activating the expression of a particular gene or set of genes, the assay can include readout to determine if the expression of the gene is reduced by the compound. Such assays can be cell-based, but more often they are enzymatic assays that can be performed in a high-throughput manner.

Step 4: Lead optimization

Lead optimization is a process that begins with a compound that displays an interesting biological action and ends with the identification of the best analog. Molecules are chemically modified and subsequently characterized in order to obtain compounds with suitable properties to become a drug. Leads are characterized with respect to pharmacodynamic properties such as efficacy and potency *in vitro* and *in vivo*, Physiochemical properties, pharmacokinetic properties, and toxicological aspects.

Potency - refers to the amount of drug required for its specific effect to occur.

Efficacy - measures the maximum strength of the effect itself, at saturating drug concentrations.

Pharmacokinetics - determines the fate of xenobiotics. It explains about "What the body does to the drug". It often divided into areas examining the extent and rate of adsorption, distribution, metabolism, and excretion (ADME).

Pharmacodynamics– It determines the biochemical and physiological effects of drugs, the mechanism of drug action and the relationship between drug concentration and effect. It explains about "What the drug does to the body".

This process ideally requires the simultaneous optimization of multiple parameters and is thus a time consuming and costly step. This is often the tightest bottleneck in drug discovery. However, by turning a biologically active chemical into an effective and safe drug, lead optimization contributes essentially towards added value in the drug discovery process.

Step 5: Pre-clinical and clinical development

Pre-clinical development: The pre-clinical development includes the following: develop large scale synthesis; animal safety studies; carcinogenicity tests; drug delivery; elimination and metabolism studies; drug formulation experiments; dose-ranging studies in animals. Wide ranging dosages of the compounds are introduced to the cell line or animal in order to obtain preliminary efficacy and pharmacokinetic information.

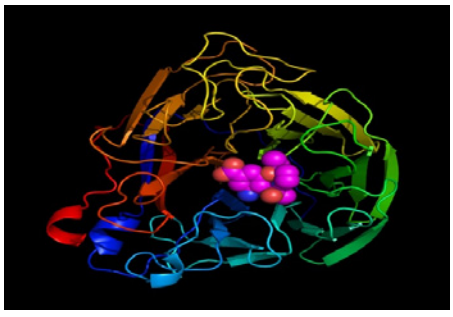

Figure 4: The best analog of lead (tamiflu) binding to the protein target (neuraminidase).

Clinical development

The NIH organizes clinical trials into 5 different types:

1. **Treatment trials**: test experimental treatments or a new combination of drugs.
2. **Prevention trials**: look for ways to prevent a disease or prevent it from returning.
3. **Diagnostic trials**: find better test or procedures for diagnosing a disease.
4. **Screening trials**: test methods of detecting diseases.
5. **Quality of life trials**: explore ways to improve comfort & quality of life for individuals with a chronic illness.

Pharmaceutical clinical trials are commonly classified into 4 phases.

Phase 0 - A recent designation for exploratory, first in human trials designed to expedite the development of promising therapeutic agents by establishing early on whether the agent behaves in human subjects as was anticipated from preclinical studies.

Phase 1 - A small group of healthy volunteers (20-80) are selected to assess the safety, tolerability, pharmacokinetics, & pharmacodynamics of a therapy. Normally include dose ranging studies so that doses for clinical use can be set/adjusted.

Phase 2- Performed on larger groups (20-300) & are designed to assess the activity of the therapy, & continue phase1 safety assessments.

Phase 3 -Randomized controlled trials on large patient groups (hundreds to thousands) aimed at being the definitive assessment of the efficacy of the new therapy, in comparison with standard therapy. Side effects are also monitored. It is typically expected that there be at lest two successful phase 3 clinical trials to obtain approval from the FDA. Once a drug has proven acceptable, the trial results are manufacturing procedures, formulation details, shelf life, etc. This document is submitted to the FDA for review.

Phase 4 - Post-launch safety monitoring & ongoing technical support of a drug may be mandated or initiated by the pharmaceutical company designed to detect rare or long term adverse effects over a large patient population & timescale than was possible during clinical trials.

Lead Discovery Methods

Leads are discovered in different ways. They can be found by pure serendipity, by systematic screening, by the chemical modification of known active compounds or by a rational approach. Actually these methods may be interconnected & progress simultaneously. An outline of the four approaches is given below:

The serendipitous pathway: Hundreds of drugs that are now in the market were discovered by unexpected observations or "lucky accidents" in everyday life or in medical clinics.

The screening pathway: Random screening is an important approach in pharmaceutical research. A great number of molecules are screened randomly in the hope of finding a compound with a specific biological activity. This approach entered a new dimension with combinatorial chemistry & high through-put screening that allows considering the chemistry & the screening in an automated manner.

The chemical modification pathway: Using this traditional method, analogs with improved biological activity are made by minor chemical modifications of known active compounds without changing their chemical backbone. The rational driving the modification is the synthetic accessibility of the molecules & the desire not to modify too much of the already known active compound.

The rational pathway: Rational drug design is a process that begins with a validated biological target, exploits the structural specificity of that target &ends with the identification of a drug candidate that optimally interacts with it & triggers the desired biological action. Genomics allows the linking of specific genes to specific diseases. Rational drug design starts with this gene information & converts it into new drug candidates.

Advanced technologies involoved in drug discovery

The following advanced technologies are involved in drug discovery process.

Genomics: The genome of the organism is the complete genetic make-up of the entire DNA complement, of that organism. Genomics, then, is the study of entire genomes. The intention of executing the sequencing and analysis of the entire human genome was to enable more rapid and effective identification of disease-associated genes and thereby provide it to drug companies with prevalidated targets. Genomic approaches have made significant advances into the discovery of functions of human genes and their involvement in diseases.

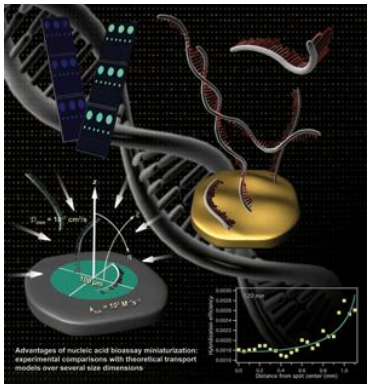

Figure 5: Genomics involved in drug discovery.

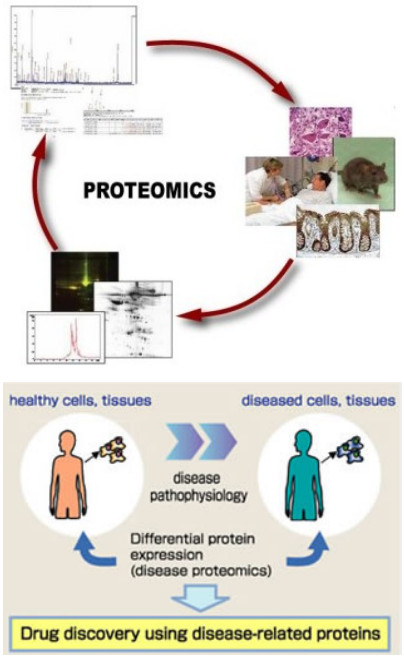

Figure 6: Proteomics involved in drug discovery.

Figure 7: Bioinformatics involved in drug discovery.

Proteomics: Proteomics is the systematic high-throughput separation and characterization of proteins within biological systems. Importantly, it is at the protein level that disease processes become manifest and at which most drugs act. Proteomics is consequently assuming a central place modern drug development with a wide spectrum of practical applications embracing diagnostic target discovery, target validation lead compound. Selection, investigation of drug modes of action, toxicology and chemical development.

Bioinformatics: Bioinformatics is having profound implications for pharmaceutical and diagnostic concerns. Structural biology and bioinformatics have assisted in lead optimization and target identification where they have well established roles; they can now contribute to lead discovery, exploiting high throughput methods of structure determination that provide powerful approaches to screening of fragment binding [9]. Bioinformatics is being increasingly used to support drug discovery process by providing functionally predictive information mined from databases and experimental datasets using a variety of computational tools.

Combinatorial chemistry: Although many disciplines and sciences play important roles in the discovery of a drug, combinatorial chemistry plays a central role because of its ability to create and produce molecules. In addition, combinatorial chemistry is an active participant in drug development from the synthesis of substances until its bulk production. Combinatorial chemistry can create large population of analogs of a given scaffold. The analogs are synthesized in successive steps with the use of robotics. The analogs are included in "combinatorial libraries" consisting of a great number of wells, each one containing in solution several dozens of compounds. Only a few milligrams of compounds can be obtained by this method, however this is generally sufficient for primary biological screening. By producing larger and diverse compound libraries, one simply increases the probability of finding novel Compounds of interesting therapeutic value.

High-throughput Screening Technique (HTS): High-throughput screening (HTS) is an approach to drug discovery that has gained widespread popularity over the last three or four years. HTS is the process of assaying a large number of potential effectors of biological activity against targets (a biological event). The methods of HTS are

Figure 8: High Throughput Screening and Combinatorial Chemistry involved in Drug.

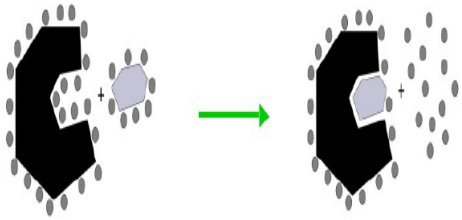

Figure 9: An Example of a drug candidate (grey colour) binding to a target (black colour). The small filled circles represent solvent (water) molecules.

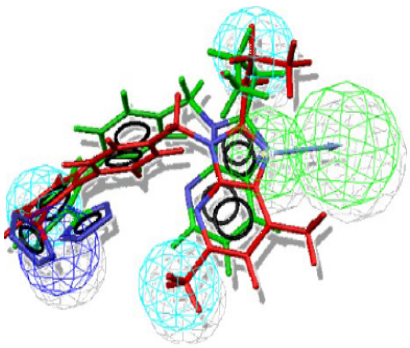

Figure 10: An example of a pharmacophore model. Spheres highlight important chemical groups that are present in both molecules (red and green sticks).

applied to the screening of combinatorial chemistry, genomics, protein, and peptide libraries [10]. The goal of HTS is to accelerate drug discovery by screening large libraries often composed of hundreds of thousands of compounds (drug candidates) at a rate that may exceed 20,000 compounds per week.

Discovery

Computational methods: Computational methods can be used to predict or simulate how a particular compound interacts with a given protein target. They can be used to assist in building hypothesis about desirable chemical properties when designing the drug and they can be used to refine and modify drug candidates. Virtual Screening (VS) is a general term for computational methods that use computers to screen a database of virtual drug candidates (called compounds) to identify promising candidates (leads) [11]. The following three advanced computational methods are used in drug discovery process.

Molecular docking

When the structure of the target is available, usually from X-ray crystallography, the most commonly used virtual screening method is molecular docking. Molecular docking programs try to predict how a drug candidate binds to a protein target without performing a laboratory experiment. It is necessary to know the geometrical structure of both the ligand and the target protein in order to use molecular docking.

Quantitative Structure-Activity Relationships (QSAR)

QSAR is an example of a method which can be applied regardless of whether the structure is known or unknown, QSAR tries to formalize what is experimentally known about how a given protein interacts with some tested compounds [12-14]. In terms of the lock and key metaphor, we do not know what the lock looks like, but we do know which keys work, and which do not. QSAR can be considered as the method of trying to build a model for why some keys work and others do not.

Pharmacophore mapping: A pharmacophore is a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity. Pharmacophore Mapping is a geometrical approach. A pharmacophore can be thought of as a 3D model of characteristic features of the binding site of the investigated protein. It may describe properties like: "In region A a positive charge is needed, in region B a hydrogen donor, region C may not be occupied…" and so on. A pharmacophore can also be thought of as a *template*, a partial description of a molecule where certain blanks need to be filled. Pharmacophore can also be built without knowing the structure of the target. This can be done by extracting features from compounds which are known experimentally to interact with the target in question. Afterwards, the derived pharmacophore model can be used to search compound databases (libraries) thus screening for potential drug candidates that may be have interest.

NMR-Based screening methods

Nuclear Magnetic Resonance (NMR) techniques are widely used in the drug discovery process. The primary feature exploited in these investigations is the large difference in mass between drugs and receptors (usually proteins) and the effect that this has on the rotational or translational correlation times for drugs bound to their targets. Many NMR parameters, such as the diffusion coefficient, spin diffusion, nuclear Overhauser enhancement, and transverse and longitudinal relaxation times, are strong functions of either the overall tumbling or translation of molecules in solution. This has led to the development of a wide variety of NMR techniques applicable to the elucidation of protein and nucleic acid structure in solution, the screening of drug candidates for binding to a target of choice, and the study of the conformational changes that occur in a target on drug binding.

Conclusion

It is extremely difficult to find new compounds that will lead to new drugs. Drug discovery is a time consuming and expensive process, the top twenty pharmaceutical companies spent ~ $16 billion on research and development every year. But, recent discovery technologies and strategies have reduced the bottleneck

in discovering high affinity ligands for therapeutic targets. The availability of biological reagents, new methods, technologies and computational tools is revolutionizing the way we do biological discovery and is enabling new approaches to identify novel targets for drug discovery and development.

Future Prospects

Today, the pharmaceutical industry is under intense pressure to generate a strong drug pipeline distinguished by better productivity, diversity and cost effectiveness. But translation of biological information to disease knowledge, validated target mechanisms, & new therapies will indeed make the coming century an era of biomedical revolution. Human ingenuity will again prove to be the pharmaceutical industry's ultimate driver in creating treatment for previously untreated diseases.

Acknowledgement

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