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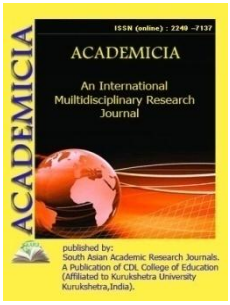

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DRUG DISCOVERY: A COMPLETE REVIEW

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ABSTRACT

The drug business is one of the main actors driving the growth of the medicines, biotechnology & pharmacology sector. Drug discovery is the process through which medicines are discovered and developed. It is a technique which aims at finding a chemical therapeutically helpful in healing & treating illness. The process of drug discovery includes the identification of candidates, synthesis, characterisation, screening & tests for therapeutic effectiveness. Once a molecule has proven its usefulness in these tests, it will begin the process of medication development prior to clinical trials. Developing a new medication is a laborious & costly endeavor, despite exciting discoveries and multibillion dollar expenditures for new drug development is silently facing turmoil. Currently, all current treatments collectively reach only about 400 distinct pharmacological targets. It is predicted that there are at least 10 times as many potential pharmacological targets that could be explored for future therapeutic treatment in the future.

KEYWORDS: *Clinical trial, Clinical trials, Drug discovery, Drug development, Potential drug targets.*

1. INTRODUCTION

Drug discovery is a procedure, which aims at finding a compound therapeutically helpful in treating and curing a condition. Typically a drug discovery effort targets a biological target that has been shown to have a role in the development of the illness or begins from a molecule with intriguing biological activity[1].

The process of drug development includes the identification of candidates, synthesis, characterisation, screening, and tests for therapeutic effectiveness. Once a molecule has proven its usefulness in these tests, it will begin the process of medication development prior to clinical

trials. Drug discovery and development is a costly process due to the high expenses of R&D and human clinical testing. The average total cost of medication development ranges from US$ 897 million to US$ 1.9 billion. The average development period is 10-15 years. The developing world bears the main burden of infectious illness, but the range of medicines available for the treatment of many infectious diseases is restricted. In the past most medicines have been found either by identifying the active component from traditional treatments or by serendipitous discovery. At now a new strategy is being tried to understand how illness and infection are regulated at the molecular and physiological level and to target particular entities based on this information[2].

2. LITERATURE REVIEW

Helmut Giersiefen in his study discloses about present and future drug development techniques and tactics are reviewed in chronological sequence throughout the drug discovery process. Many of these methods are discussed in greater depth in the other chapters of this book. We refer only to tiny organic compounds and not therapeutic proteins ("biologicals"), for which the situation may be very different[3].

J Drews in another study discloses about the emergence of molecular biology and, in particular, of genomic sciences is having a profound effect on drug development. Recombinant proteins and monoclonal antibodies have significantly expanded our therapeutic armamentarium. Genome sciences, coupled with bioinformatic techniques, enable us to analyze the genetic foundation of complex illnesses and to identify the most appropriate areas of attack for future medications, thus expanding the number of therapy choices. The significant rise in the complexity of drug development is imposing changes in the institutional foundation of this multidisciplinary effort. The biotech sector is establishing itself as the discovery arm of the pharmaceutical industry. In bridging the gap between academia and big pharmaceutical corporations, the biotech firms have proven successful vehicles of knowledge transfer[4].

Shenliang Wang in yet another study discloses about reliable methods for addressing target identification and validation are the basis of effective medication development. Microarrays have been widely used in genomics/proteomics methods for gene/protein expression profiling and tissue/cell-scale target validation. Besides being used as an essential step in analyzing high-throughput experiments such as those involving microarrays, bioinformatics can also contribute to the processes of target identification and validation by providing functional information about target candidates and positioning information to biological networks. Antisense technologies (including RNA interference technology, which is lately extremely 'hot') allow sequence-based gene knockdown at the RNA level. Zinc finger proteins are a DNA transcription-targeting form of knockdown. Chemical genomics and proteomics are developing techniques for producing phenotypic alterations, thereby leading to target and hit identifications. NMR-based screening, as well as activity-based protein profiling, are attempting to fulfill the need of high-throughput target discovery[5].

3. DISCUSSION

1.1Step 1: Target identification:

Target identification is the first important step in the drug discovery pipeline. Generally speaking, a drug target is the particular binding site of a drug in vivo via which the molecule performs its effect. A specific pharmacological target may have the following characteristics:

- The therapeutic target is a biomolecule(s), usually a protein that could exist in solitary or complex form.
- The biomolecules have unique places that match other.
- The biomolecular structure may alter when the biomolecule binds to tiny molecules and the changes in structure normally are reversible.
- Following the change in the biomolecule's structure various physiological reactions occur and cause control of the cell, organ, tissue, or body state.
- The physiological reactions produced by the changes in biomolecule structure play a significant part in complicated regulation and have a therapeutic impact on pathological diseases.
- The expression, activity, and structure of the biomolecule might change throughout the course of the disease process.
- Small molecules attaching to the biomolecules are medicines.

As is clear from the preceding explanation, a therapeutic target is a key molecule engaged in a particular metabolic or signal transduction pathway that is unique to a medical state or a specific illness. However, the phrase 'drug target' itself has many limits and is debated within the pharmaceutical industry. In this regard, 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 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-toone.

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 therapeutic target typically refers to a specific biomolecule. According to whether there are medicines available, a drug target can be divided 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 medicines targeting this target. The latter are those biomolecules whose activities are not fully understood and which lack medicines targeting them. Potential targets offer possibilities for entirely new therapeutic development[6].

1.2 Step 2: Target Validiation:

New target validation is the foundation of totally new drug exploration and the first stage of drug development.

New drug target validation may be of tremendous assistance not only to new drug research and development but also offer additional insight into the pathophysiology of target associated illnesses [3]. Basically, the target validation process can comprise six steps:

1. Discovering a biomolecule of interest.

2. Evaluating its potential as a target.

3. Designing a bioassay to assess biological activity.

4. Constructing a high-throughput screen.

5. Performing screening to discover hits.

6. Evaluating the hits.

The drug discovery process begins with the identification or growing evidence of, biological targets that are thought to be connected to a specific disease or pathology. Information supporting the involvement of these targets in disease modulation may come from a number of sources [4]. Traditionally, the targets have been researched and mainly found in university labs, and to a lesser degree in the laboratories of pharmaceutical and biotechnology companies. Primary research into understanding the fundamental, essential mechanisms for communication inside and between cells and their disruption in circumstances has been the basic method for establishing prospective targets appropriate for therapeutic intervention[7].

1.3 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 cellbased 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 done mainly using knock-out or knock-in animal models; small molecule molecular target in vitro typically precedes the validation of the therapeutic idea in vivo; combined this defines its clinical potential. Validation includes research in molecular target in vitro typically progresses with the target protein and modify its activity. Libraries of substances that are either synthetic chemicals, peptides, natural or designed proteins, or antibodies are exposed to the target in a way that will identify and isolate those members of the library that interact with and, ideally, have an impact on the target [5-8]. The chemicals chosen are termed "leads". Initially screening may be done by looking for compounds that bind to the target, however binding is not sufficient for therapeutic action. More recent screening methods incorporate an activity-based readout as part of the first screening test. For example, if the aim is to block a protein that is involved in triggering the expression of a particular gene or group of genes, the assay may include readout to determine whether the expression of the gene is decreased by the chemical. Such assays may be cell-based, but more frequently they are enzymatic assays that can be conducted in a high-throughput way for compounds that bind to the target, but binding is not sufficient for therapeutic action. More modern screening methods incorporate an activity-based readout as part of the first screening test. For example, if the goal is to block a protein that is involved in triggering the expression of a specific gene or group of genes, the assay may include readout to determine whether the expression of the gene is decreased by the chemical.

Such assays may be cell-based, but more frequently they are enzymatic assays that can be conducted in a high-throughput way[8].

1.4 Step 4: Lead Optimization:

Lead optimization is a procedure that starts with a compound that exhibits an intriguing biological activity and concludes with the identification of the best analog. Molecules are chemically modified and then analyzed in order to produce molecules with suitable characteristics to become a medication. Leads are evaluated with respect to pharmacodynamic characteristics such as effectiveness and potency in vitro and in vivo, Physiochemical properties, pharmacokinetic properties, and toxicological aspects.

Potency - refers to the quantity of medication needed for its specific effect to occur.

Efficacy - quantifies the maximal intensity of the effect itself, at saturating medication concentrations.

Pharmacokinetics - influences the destiny of xenobiotics. It explains about "What the body does to the drug". It typically divided into sections evaluating the amount and rate of adsorption, distribution, metabolism, and excretion (ADME) (ADME).

Pharmacodynamics–It defines the biochemical and physiological effects of medicines, the mechanism of drug action and the relationship between drug concentration and effect. It talks about "What the medication does to the body".

This procedure ideally involves the simultaneous optimization of multiple parameters and is therefore a time intensive and expensive phase.

This is typically the tightest bottleneck in drug discovery. However, by turning a physiologically active molecule into an effective and safe drug, lead optimization contributes significantly towards added value in the drug development process[9].

1.5 Step 5: Pre-clinical and clinical development:

Pre-clinical development: The pre-clinical development includes the following: create large scale synthesis; animal safety research; carcinogenicity testing; drug delivery; elimination and metabolism studies; drug formulation experiments; dose-ranging studies in animals. Wide range doses of the compounds are introduced to the cell line or animal in order to gather preliminary effectiveness and pharmacokinetic information.

The NIH divides clinical trials into 5 distinct types:

- Treatment trials: evaluate experimental therapies or a new combination of medicines.
- Prevention trials: seek for methods to prevent an illness or prevent it from recurring.
- Diagnostic trials: discover improved test or methods for diagnosing a disease.
- Screening trials: test ways of identifying illnesses.
- Quality of life trials: investigate methods to enhance comfort & quality of life for people with a chronic disease.

Pharmaceutical clinical trials are usually divided into 4 stages.

Phase 0-A recent classification for exploratory, first in human trials intended to accelerate the development of potential therapeutic agents by demonstrating early on whether the drug behaves in human subjects as was expected from preclinical research.

Phase 1-A small sample of healthy volunteers (20-80) are selected to evaluate the safety, tolerability, pharmacokinetics, &spharmacodynamics of a treatment. Normally include dosage ranging studies so that doses for clinical usage may be set adjusted.

Phase 2-Performed on bigger groups (20-300) & are designed to evaluate the activity of the treatment, & continue phase1 safety assessments.

Phase 3-Randomized controlled trials on large patient groups (hundreds to thousands) aiming at becoming the final evaluation of the effectiveness of the new treatment, in contrast with conventional therapy.

Side effects are also examined. It is generally anticipated that there be at least two successful phase 3 clinical studies to gain approval from the FDA. Once a medication has proved acceptable, the trial results are manufacturing methods, formulation information, shelf life, etc.

This material is submitted to the FDA for evaluation.

Phase 4 - Post-launch safety monitoring & continuing technical support of a medication may be required or started by the pharmaceutical company intended to identify uncommon or long term side effects across a large patient population & timeframe than was feasible during clinical trials[10].

4. CONCLUSION

It is very challenging to discover novel chemicals that will lead to new medicines. Drug discovery is a time demanding and expensive process, the top twenty pharmaceutical firms spend ~ $16 billion on research and development per year. But, recent discovery methods and techniques have decreased the bottleneck in finding high affinity ligands for therapeutic targets. The availability of biological reagents, new techniques, technologies and computational tools is changing the way we conduct biological discovery and is allowing new ways to find novel targets for drug discovery and development.

Today, the pharmaceutical sector is under tremendous pressure to generate \sa robust medication pipeline characterized by improved productivity, variety and cost effectiveness. But conversion of biological information to disease knowledge, validated target mechanisms, & novel treatments will certainly make the coming century an age of biomedical revolution. Human creativity will again prove to be the pharmaceutical industry's ultimate engine in finding therapy for previously treatable illnesses.

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