Drug Discovery, Drug Development and Expensive Failures

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***Abstract*: Earlier herbs were used to cure diseases. In 19th century, the concept of drug discovery and drug development was evolved. Drug development is the method of introduction of a brand new drug into the market once the lead compounds are identified through the method of drug discovery. The paper will begin with briefly introducing the process of drug discovery and drug development. It will describe the various stages involved in the process beginning from choosing the disease to clinical trials being carried out. Furthermore, it will delve into the question as to why drug developments are identified as expensive failures.**

***Index Terms*: Drug Discovery, Drug Development, Target, Lead Compounds, Receptors, Enzymes, Drug, Pharmaceutical Company, Clinical Trials**

I. INTRODUCTION

Before the 20th Century medicines consisted of herbs. It was in mid-19th century that serious efforts were made to isolate and purify the active compounds called lead compound from these natural products. Scientists synthetically made drugs similar to herbs for curing lives of millions of people. Chemists made synthetic efforts to make thousands of analogues similar to what nature had provided. In 1873, organic chemists in Germany synthesized dyes which gave way to pharmaceutical industry. Further, leading the path towards drug discovery and drug development. The recent advances in medicinal chemistry and better understanding of the functioning of the body at cellular and molecular level gave a boost to the research being carried out in the pharmaceutical industry. The research begins with the identification of a target molecule and designing a drug competent to interact with that target resulting in minimum side effects.

With increasing research and development, various advancements, knowledge of genomics, comprehension of the disease at molecular level and easy and convenient availability of data have given way to the expansion in drug discovery and development. Though research and development are substantially in progress, but the number of drugs approved by the Food and Drug Administration (FDA) is not very high leading to drug development being recognized as a field of expensive failures.

II. STAGES IN DRUG DISCOVERY AND DRUG DEVELOPMENT

There are multiple stages involved in the process of drug discovery and drug development. The preliminary stage involves selection of a disease and finally ends with clinical trials and procurement of patent in case of a successful trial.

Choose a Disease

The process begins with identification of a disease by a pharmaceutical company for which there is a demand for a new drug. The companies are driven by the motive of good financial returns for their investment. As a result, the research projects for the designing of a new drug is carried out on diseases such as migraine, depression, obesity, flu, cancer and cardiovascular diseases as these are more common diseases with a high demand for drugs instead of tropical diseases with a low demand for drugs.

Choosing Drug Target

Once the particular area of medicinal need (disease) has been determined a suitable drug target (receptor, enzyme) has to be identified. This is a very important step, as drug reacts with the enzymes involved. Therefore, before talking of drug target we should know the molecular structure of target with which it would react. An example of developed drug targets are CASPASES (enzymes). Caspases act as catalyst in the process of hydrolysis of cellular proteins. product formed results in inflammation and cell death. We know cell death is a natural phenomenon taking place in our body, without these enzymes there would be unregulated growth resulting in disease like cancer.

Further, this property of caspases which catalyzes the hydrolysis of proteins can be also used by pharmacologists to produce new therapies for a variety of diseases requiring cell death like cancer and certain viral infections.

Target Specificity and Selectivity between Species

Target specificity and selectivity are important features of modern medicinal chemistry. The more selective the drug for the target, more likely that it will interact with the specific target and less chance that it will give undesired side effects. The best targets are those which are unique to the disease-causing microbes. If we take the drug, Penicillin into consideration, it only targets the enzyme which is involved in the biosynthesis of bacterial cell wall. However, the cells of mammals do not have cell walls, so this enzyme is absent in humans and thus the drug (Penicillin) acts only on these bacteria and has no side effects on humans.

Target specificity and selectivity is also essential for drugs interacting with their own enzymes. Few drugs acting as enzyme inhibitors should be selective in nature ensuring that they only inhibit the activity of target enzyme and not some other enzyme.

Choice of Test System (BIOASSAY)

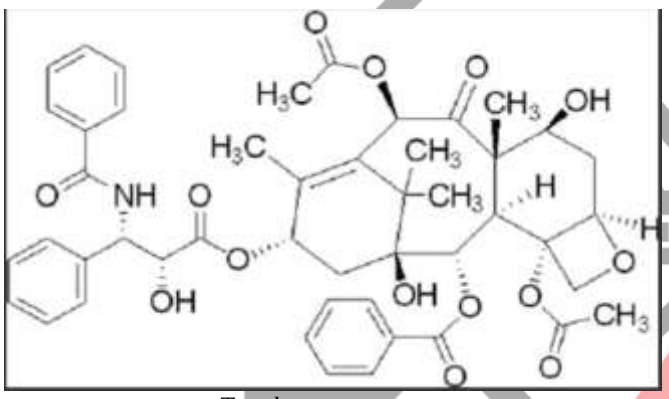
Choosing a right test system is very crucial in the success of drug development. Human testing cannot be done at an early stage and so the test must be done in vitro (isolated cells and tissues) or in vivo (on animals). In vivo test, the animal is treated and is under observation to see whether the drug eliminates the observable systems. There are several problems associated with in vivo testing. Such testing is very slow and causes animal suffering. If a negative result is observed, then it is difficult to tell whether it is due to the drug failing to bind with the target or the drug not reaching the target at all? Number of times many drugs which proved effective in animal testing were ineffective in clinical trials. For example, Penicillin Methyl Ester are hydrolyzed in the mouse or rat to produce Penicillin but not hydrolyzed in rabbit, dog or man.

Screening under Nuclear Magnetic Resonance

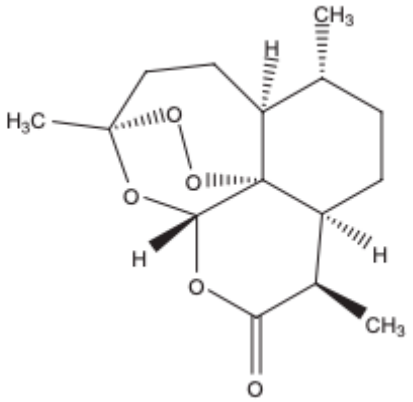
Nuclear Magnetic resonance (NMR) spectroscopy can be used to detect whether a compound binds to an enzyme/receptor target. In NMR spectroscopy, when the nuclei relax to the ground state from the excited state it gives off energy. This energy is used to produce a spectrum. The time taken by different nuclei to relax from their excited state to their ground state is called the relaxation time. The relaxation time varies based on the size of the molecule. Small molecules such as drugs have long relaxation time whereas large molecules have small relaxation time and thus the measurement of small molecules is only possible. First the NMR spectrum of the drug is taken followed by the addition of the protein and then the spectrum is rerun resulting in short relaxation time as now the molecule (drug and protein) becomes large and signals are not detected.

If the drug fails to bind with the protein, then its NMR spectrum is still detected. If the drug binds it becomes a part of the protein and as a result the nuclei will have a short relaxation time and no NMR spectrum will be detected. Once the target and a testing system have been chosen, the next stage is to find a lead compound, which shows the desired pharmaceutical activity.

Many natural products are biologically active compounds and are used as lead compound e.g. morphine, cocaine, quinine. Useful drugs which have been isolated and identified are Taxol from the Yew tree and anti-malarial agent Artemisinin from a Chinese plant.



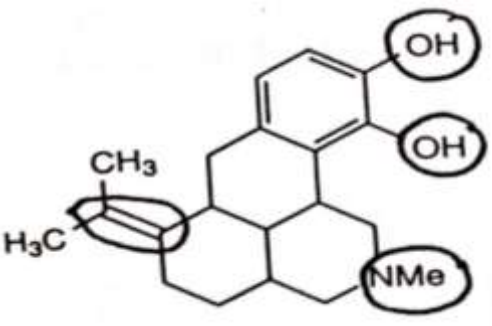
Taxol



Artemisinin

Many drugs are obtained from marine sources like corals and sponges as they have chemicals with anti-inflammatory and anti-cancer characteristics. Certain venoms and toxins from animal, plants, insects and microorganisms can be used as lead compounds. For example, teprotide is a peptide which when isolated from the venom of the Brazilian Vipor was used as lead compound for the development of anti-hypertensive agents namely, cilazapril and captopril.

The lead compounds which are discovered, their structure determination can be done by NMR, Infrared Spectroscopy or X-ray crystallography. Once the structure of the compound is established, the next aim is to study which parts of the molecule are biologically active and which are not. Let us take a compound isolated by a chemist, a natural product called Glipine. It has a variety of groups present, which can act as potential binding sites. We can replace these groups by other groups and study its biological activity.



Glipine

If we alter the hydroxyl group to a methyl ether or ester, then we weaken or destroy the hydrogen bond.

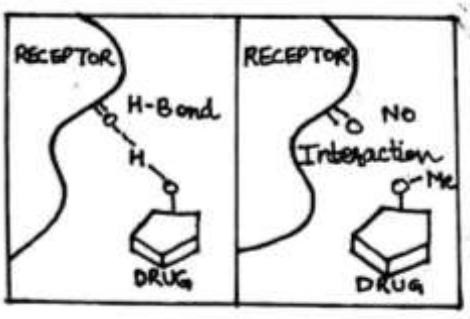


Figure 1

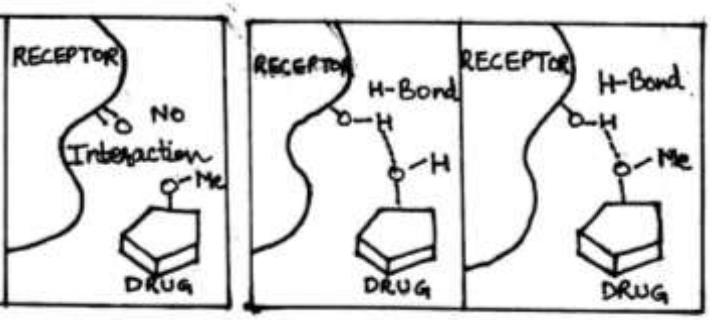


Figure 2

In Figure 1, the proton of hydroxyl group of the drug is involved in hydrogen bonding with the receptor. If the proton is replaced by the methyl group then the hydrogen bond is lost. In Figure 2, the oxygen atom of the drug forms a hydrogen bond with the amino acid residue. On replacing the proton by methyl group, the oxygen is still present in ether analogue of the drug and now the bonding is between oxygen of ether and hydrogen of amino acid residue. In this, the hydrogen bonding is weak due to shielding by the methyl group.

Target Oriented Drug Design

Once the important binding groups have been identified it is possible to synthesize analogues of the lead compounds. The medicinal chemists are developing drugs with four objectives in mind:

1. to increase activity;
2. to reduce side effects;
3. to provide easy and efficient administration to the patient; and
4. for ease of synthesis.

Target oriented drug design aims to modify the lead compound such that it interacts more effectively and selectively with its target in the body and thus increases the activity of the drug. Stronger the drug-target interactions, higher the activity of the drug and an increase in target selectivity will lower the side-effects.

Pharmacokinetic Drug Design

The compound with the best interactions is not necessarily the best drug to use in medicine. Some of the most active drug discovered in vitro show no activity in vivo. This is because clinically useful drug has to travel through the body to reach its target. There are many barriers which can prevent a drug reaching its target. Pharmacokinetic drug design focuses on developing such a drug design which can overcome these barriers.

Drug Metabolism

When drugs enter the body, they are attacked by a whole range of metabolic enzymes whose role is to degrade them so that they can be excreted. If the drug is found to be polar, it will be excreted by the kidneys. On the other hand, non-polar drugs are not easily excreted. The objective of drug metabolism is to convert non-polar compounds into polar compounds which can be easily excreted. Certain enzymes in liver (cytochrome P450) can carry out oxidization in drug and are able to add polar hydroxyl group which can be excreted out.

Drug Toxicity

Drugs should be tested on animals and finally on humans to see what metabolites (end products) are formed in drug metabolism. This is a safety issue, since it is important to ensure that no toxic metabolites are formed. The end products in drug metabolism should be inactive or dormant in nature and removed from the body easily.

This is a very important steps in drug design. On several occasions it has been found a drug which is active in vivo (animals) is inactive in vitro. As a result, the pharmacologists face a new problem as during the development of the drug, a difference in activity of the drug in vivo and in vitro could not be anticipated. For example, when thalidomide was developed nobody appreciated that drugs could cause foetal deformities and so there was no test for this. It should be borne in mind that it is rare for a drug to be 100% pure. Minor impurities are bound to be present arising from the synthetic route. The toxicity effect arising from a drug synthesized by one route is not the same for the drug prepared by another synthetic route. Finally, it is unlikely that the thorny problems of animal testing will disappear. There are so many variables involved in drug interactions in the body that it is impossible to anticipate them all. One must consider that drug will be metabolized to other compounds which have their own range of biological properties and side-effects. It is impossible to predict whether a potential drug will be safe in in-vitro alone. Here lies the importance of animal testing. Only animal test can test for the unexpected, unless we are prepared to volunteer ourselves as guinea pigs. Animal experiments will remain an essential feature of drug development for many years to come. Though unfortunate but experimenting on animals will always be an important part of drug discovery and drug development.

Clinical Trials

Clinical trial involves testing the drugs on volunteers and patients and it involves four different phases.

Phase I

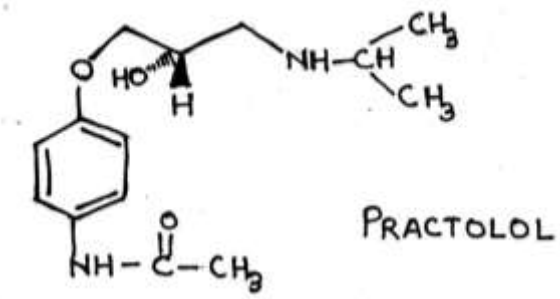
It is given to healthy volunteers to test the drug potency, pharmacokinetics and side-effects.

Phase-II

It is tested on small groups of patients to see if it has any side effects and to find out what dose levels should be used.

Phase III

The drug is tested on a larger sample of patients and compared with others available treatments (preparation which has no side effects). This establishes whether the drug is effective or not. It also helps in finding out the right dosage. Any side effects not previously detected may be picked up with a large sample of patients. If the drug succeeds in passing phase III, it can be licensed and marketed.



Phase IV

The drug is now placed in the market and doctors prescribe them to their patients. However, the drug is still monitored for its effectiveness and for unexpected side-effects. This phase is a never-ending process since unexpected side-effects may crop up many years after the introduction of the drug. For instance, the β- blocked practolol had to be withdrawn after several years of use since some patients suffered blindness and even death.

Patents

Having spent enormous amounts of time and money on research and development, a pharmaceutical company wants to recoup its cost and reap the benefits of all its hard work. To do so, it needs the right to sell and manufacture its products for a reasonable period and price which recoup its costs and generate profits. Patents allow the companies to gain these rights.

III. EXPENSIVE FAILURES

Drug discovery is time consuming, risky, tedious and expensive as it involves huge investment of funds by pharmaceutical companies. It takes almost 100 million to 1 billion dollars to launch a new drug and the time taken is approximately twelve years. The only way to lower the cost and time in drug discovery is to reduce the failure of procedures at different stages of experiment. An analysis in the field of drug discovery and development shows that the hundreds of drugs comprising New Molecular Entity (NME) are tested but only few of them become marketed product. The data obtained for drug approval from Central Drug Standard Control Organization, India shows that the number of drugs approved in the year 2018 were 6, in 2019 were 7 and till September, 2020 were 9. Thus, it is extremely discouraging and deincentivizing for the pharmaceutical companies and the scientists as there is not much progression in the number of drugs approved including NMEs. An answer to this is that as the cost of research and development is very high, more money has to be pumped in for carrying out new projects without any money crunch. Secondly, the education policies are such, that the universities students in the field of bio-sciences are working on high budget drug development projects however they are not using the advanced technologies like High Throughout Screening Process (HTS) for the research. Thirdly, the supply of approved drugs has gone down as the funding of the research institutions involved in medicinal chemistry has decreased due to the dwindling economies. As a result, there are lay-offs, and the young scientists are compelled to leave their jobs and work on other scientific researches not related to drug discovery and development.

One of the ways to reduce the expensive failures is by ensuring that the researchers and scientists are aware of the advancements like genomics and upcoming technologies like HTS and making use of them for drug discovery and its development.

IV. CONCLUSION

Drug discovery and development is a continuously evolving process. Initially, it started with the isolation and purification of active compounds from natural products. Now, it is a long process involving various stages. Today, the research in pharmaceutical industries begins with identifying a suitable target and designing a drug to interact with the target and finally ends with the clinical trials. The process of drug discovery and development is expensive and time consuming. Further, all drugs do not get approved easily by the FDA and as a result, this field witnesses a lot of expensive failures.

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