DRUG DESIGN-DISCOVERY & DRUG DEVELOPMENT

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Abstract :

This review article deals with the different steps involved in designing and developing of drugs. A brief history of how drugs have been developed for the past century has been traced. Different techniques involved with modern day drug designing along with how the drug interacts with the biological system to combat diseases are also discussed. The role of combinatorial chemistry and computer aided drug designing brings about the successful manufacture of a drug molecule. This drug molecule is then subjected to various tests both through modelling and real world experiments. After those procedures preclinical trials establish the efficacy of the drug .Lastly how a drug is ultimately brought to the market has been discussed in this article.

Key words: drugs, combinatorial chemistry , proteomics , CADD, pharmaco vigilance

Introduction : A pharmaceutical drug, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being. Drugs have been used from time immemorial by almost all ancient civilizations in the world. Archaeological evidence indicates that even during the stone ages human beings were using certain plants for medicinal purposes. The first recorded drug was opium .Opium and its extracts was used mainly for its analgesic properties , though people became aware of its harmful addiction causing nature in the long run. In fact the best definition of a proper medicine comes from *Charak Samhita* 'That medicine is a right one and pure one which cures a disease –physical, mental, spiritual- and does not give rise to adverse reactions and does not create other disease.' Drug designing and development even in this twenty first century must be made following that most important axiom stated first by Hippocrates the father of medicine (***460-355 BC)*** "First do no harm".

Drug Design

Drug design, often referred to finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bio-molecular target with which they interact and therefore will bind to it.

Drug development

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research and clinical trials on humans, and regulatory approval with a new drug application to market the drug.

Drug delivery

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body in desired concentration at a particular target tissue to produce therapeutic effect. Some of the common routes of administration include the enteral (gastrointestinal tract), parenteral (via injections), inhalation(via vapours) , trans dermal(through the skin). Chemically many drugs are nano particles, soluble in fat, which could be administered through topical and oral routes.

Drug discovery

In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery. We can take the example of curcumin the active ingredient of Turmeric or Haldi. In India we had known the health benefits of turmeric since time immemorial. Curcumin is the main active ingredient in turmeric. It has powerful anti-inflammatory effects and is a very strong antioxidant. Modern scientific research has shown it to be effective in preventing heart disease and even spread of a certain kind of cancer.

But now from thorough medical research we know that diseases are controlled at molecular and physiological level by certain bioactive molecules. Chemistry is indispensible in knowing the structure of these molecules in the atomic level.

History of Drug Discovery

The history of drug discovery can be traced through the decades of the past century through the following steps

Pre 1919

- Herbal Drugs
- Chance discoveries

1920s, 30s

- Vitamins
- Vaccines

1940s

- Antibiotic Era
- Research & Development boost due to World War 2

1950s

- New technology,
- Discovery of DNA

1960s

- Breakthrough in Etiology ; investigation of the cause, set of causes, or manner of causation of a disease or condition.

1970s

- Rise of Biotechnology
- Use of Information Technology

1980s

- Commercialization of Drug Discovery
- Combinatorial Chemistry

1990s

- Robotics
- Automation

Techniques of Drug Discovery

The older approaches to drug discovery was subjecting natural products with proven medicinal properties to pharmacological evaluations. Sometime using the synthetic techniques of organic Chemistry analogues of these herbal drugs were prepared in the laboratory either to increase the efficacy of the drug or make it more easily available. Repurposing of drugs is a very prevalent technique even today , in fact the drug used to treat kala azar is now being repurposed to combat the rising cases of mucormycosis.

The newer approaches to drug discovery includes

- Molecular Modelling- CADD(Computer aided drug design)
- Biotechnology & Recombinant DNA Technology-
- Combinatorial Chemistry-

Target Identification

- Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease.
- Scientists use a variety of techniques to identify and isolate individual targets to learn more about their functions and how they influence disease.
- Compounds are then identified that have various interactions with the drug targets that might be helpful in treatment of a specific disease.

Target Selection

- Target selection in drug discovery is defined as the decision to focus on finding an agent with a particular biological action that is anticipated to have therapeutic utility . It is influenced by a complex balance of scientific, medical and strategic considerations.
- Target identification is required to identify molecular targets that are involved in disease progression.
- Target validation is important to prove that manipulating the molecular target can provide therapeutic benefit for patients.

Two modern approaches used for target identification and selection are genomics and proteomics

Genomics is that branch of Science that studies human genes through sequencing the DNA in our chromosome. Each gene in the human body codes for a particular protein besides being linked to several other proteins, hence from genomics it can be assumed that the number of potential drug targets may lie between 5,000 and 10,000. Proteomics on the other hand deals with study of proteins. It is at the protein level that disease processes become manifest, and almost all (91%) drugs act by binding reversibly or irreversibly to these proteins. Target identification with proteomics is performed by comparing the protein expression levels in normal and diseased tissues.

Lead Identification

- A lead compound or substance is one that is believed to have potential to treat disease.
- Laboratory scientists can compare known substances with new compounds to determine their likelihood of success.
- Leads are sometimes developed as collections, or libraries, of individual molecules that possess properties needed in a new drug.

- Testing is then done on each of these molecules to confirm its effect on the drug.

Ways to find a lead compound

- **Nature** – bacteria, moulds, plant *extracts.* This is a very popular and quite a time tested technique which resulted in the discovery of the antibiotic penicillin from the fungus *Penicillium notatum*. However now biotechnology is used instead ; scientists can genetically engineer living systems to produce disease-fighting biological molecules.
- **De Novo** – scientists can also create molecules from scratch – computer modelling
- **High throughput screening** – test thousands of compounds against the target to identify any that might be promising.
- **Combinatorial Chemistry** : Rapid synthesis of a large number of different but structurally related molecules identified through computer simulation.
- **Assay Development** It is used for measuring the activity of a drug. By discriminating between different compounds obtained through combinatorial chemistry. It is used to evaluate the expression in protein targets and enzyme/ substrate interactions.
- **Computer-aided drug design (CADD)** uses computational approaches to discover, develop, and analyze drugs and similar biologically active molecules. The ligand-based **computer-aided drug** discovery (LB-CADD) approach involves the analysis of ligands known to interact with a target of interest.
- Quantitative structure–activity relationship models **(QSAR)**: It is a strategy of essential importance for chemistry and pharmacy, based on the idea that when we change a structure of a molecule then also the activity or property of the substance will be modified. It is a computer based regression study.
- **DOCKING:** Receptor-ligand interaction study , which establishes the level of interaction between the lead compound and the causative agent through computer simulation.

Lead Optimization

- Lead optimization compares the properties of various lead compounds and provides information to help biopharmaceutical companies select the compound or compounds with the greatest potential to be developed into safe and effective medicines.
- Often during this same stage of development, lead prioritization studies are conducted in living organisms (*in vivo*) and in cells in the test tube (*in vitro*) to compare various lead compounds and how they are metabolized and affect the body.

Early safety tests

- Lead compounds go through a series of tests to provide an early assessment of the safety.
- Scientists test **Absorption, Distribution, Metabolism, Excretion and Toxicological** (ADME/Tox) properties, or "pharmacokinetics," of each lead compound .

Successful drugs must be:

- absorbed into the bloodstream properly ,
- distributed to the concerned site of action in the body,
- metabolized efficiently and effectively,
- successfully excreted from the body and
- Demonstrated to be non toxic.

QSAR comes in helpful for identification of the pharmacophore. Pharmacophore is the precise section of the molecule that is responsible for biological activity. This enables to prepare more active compound and allow elimination of excessive functional groups, so as to increase the efficacy of the drug. Another important tool is **in silico screening.** Broadly, **in silico means** biological experiments conducted on a computer or via computer simulation. **In silico screening** uses virtual **screening** tools to make predictions about the behaviour of different compounds. It achieves that by modelling the interactions between chemical molecules and their biological targets.

After computer simulation studies are completed , in vitro studies are performed. In vitro studies generally involve actual biochemical analysis made in a wet lab like enzyme assays , cell culture assays and tissue culture assays. Only after these tests give successful results the drug development progresses to the pre-clinical state.

Pre Clinical Studies

At the Pre-clinical stage, the regulatory bodies generally ask about three things .They are

1. **Pharmacological Testing :** This is a procedure to find out how effective the drug is in the remission of the disease in an actual organism, most often rabbits, mice and guinea pigs are used for this kind of testing.
2. **Toxicological Testing** : To determine the acute toxicity of the drug in at least two species of animals. The tolerance level of the drug along with side effects in all aspect of health including reproductive performance is studied for the animal.

3. **Pharmacokinetic Testing :**This includes study of the physio-chemical properties of the drug and how best to administer the drug including the designing of dosage forms. The shelf life of the drug and how long it will take to expire is also studied here.

Clinical Development of Drug

This is the last and the most time consuming stage in drug development. It begins with Investigational New Drug Application (IND). IND application is a result of a successful pre-clinical development program and with this a researcher advances to the clinical trials on human beings with the new drug so developed . The process of clinical trials in drug development goes through at least five different phases, progressing from phase 0 to phase IV. The study begins with micro dosing of 50 to 100 healthy volunteers ,till in phase IV where close monitoring is done both by the health care providers and the drug regulatory agency to the effects of the drug and its compliance to the patient in the long run once it is in the market. After completion of phase III , the trial addresses the following issues

- Adverse Reactions in large group of patients over a longer period of exposure .
- The ideal dosage regimen.
- Should the drug be allowed in the market.
- Most pharmaceutical companies go for New Drug Application (NDA) after completing phase III and while continuing through the process of phase IV.

Phase IV is involved with

a) Post Marketing Surveillance.

b) Designed to detect any rare or long-term adverse effects.

c) Adverse Drug Reaction Monitoring (Pharmacovigilance)

The whole process can take from 3 to 7 years.

Conclusion

The pharmaceutical industry is one of the most important industries in the world with astronomical sums of money invested in it. This hardly comes as a surprise; as medicine is the one thing which we could not do without. Curbing infant mortality , enhancing the quality of life we lead , increasing life expectancy , medicines have a lot to contribute to the general wellbeing of the entire human race. The extensive research and painstaking labour which goes into development of a particular drug has all branches of Science ranging from Statistics to Biology , with Physics , Computer science and Chemistry thrown in between , involved. Economics , politics and social science dictate the development of the drug by its decision making , release of funds , promotion of drugs . However one thing should be kept in mind , specially after our experience with COVID-19 pandemic

which has wrecked such a havoc throughout the globe, development of drug is not a straightforward process, constant monitoring is required in every phase . It goes without saying the multitude of drugs which has been developed to combat the coronovirus SARS-CoV-2 in such a short time span needs a constant stringent pharmacovigilance throughout the coming years.

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This article is transcribed by the editorial board from a lecture given in the Webinar titled 'Pharmaceutical Chemistry' jointly organized by Basanti Devi College and the Undergraduate board of studies in Chemistry of Calcutta University , it was held on 6th June 2020.