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Review Article

A REVIEW ON DRUG DISCOVERY TO APPROVAL PROCESS

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A R T I C L E I N F O

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A B S T R A C T

A pre-discovery stage in which basic research is performed to try to understand the mechanisms leading to diseases and propose possible targets (e.g., proteins).the drug discovery stage, during which scientists search for molecules (two main large families, small molecules and biologics) or other therapeutic strategies that interfere or cure the investigated disease or at least alleviate the symptoms. the preclinical development stage that focuses on clarifying the mode of action of the drug candidates, investigates potential toxicity, validates efficacy on various in vitro and in vivo models, and starts evaluate formulation. The clinical stage that investigates the drug candidate in humans. The reviewing, approval and post-market monitoring stage during which the drug is approved or not. In practice, finding new treatments is very challenging. Despite advances in the understanding of biological systems and the development of cutting-edge technologies, the process is still long, costly with a high attrition rate. New approaches, such as artificial intelligence and novel in vitro technologies, are being used in an attempt to rationalize R&D and bring new drugs to patients faster, but several obstacles remain. Our hope is that one day, it becomes possible to rapidly design inexpensive, more specific, more effective, non-toxic, and personalized drugs. This is a goal towards which all authors of this article have devoted most of their careers.

Introduction

Drug discovery has a long history and dates back to the early days of human civilization. In those ancient times, treatments were often discovered by chance or resulted from observation of nature, typically but not exclusively, using ingredients extracted from plants/animals, and not just used for physical remedy but also for spiritual healing. Modern drug discovery research started to being performed around the early 1900s. Nowadays, the development of a new medicine usually starts when basic research, often performed in academia, identifies a macromolecule (i.e., a molecule with a large molecular weight like genes/proteins), or a dysfunctional signaling pathway or a molecular mechanism apparently linked to a disease condition. To be nominated therapeutic target, scientists will also have to find therapeutic agents that modify the function of the perturbed target and restore health or alleviate symptoms. Finding the right target is however extremely challenging.

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Further, drugs are efficient in humans because of specific actions on the intended therapeutic target but also due to interactions with other, unintended (often unknown) targets! The process continues with the search of therapeutic agents followed by a preclinical phase, during which potential drugs are tested in a battery of animal models, to demonstrate safety and select drug. The studies are then submitted to regulatory agencies, which review the documents and decide about market approval. If the review is positive, the drug can then be released to the market and be administrated to patients.

Once a drug has been approved, investigations continue to monitor putative side effects that could be caused, over time, by the new treatment. This last step is often referred to as Pharmacovigilance studies (or real-world evidence), generally dubbed “phase 4” clinical trial. The entire drug discovery and development process involves many disciplines, years of efforts and is very expensive. It also implies the generation and use of vast amount of data usually obtained via different types of high-throughput technologies.

Many of these experiments and the analysis of the results can be automated via computer-assisted methods to speed-up some steps of the process, gain knowledge and reduce mistakes. As mentioned above, to act on a disease, the problematic targets have to be modulated by a therapeutic agent or several.

There is a wide variety of agents that traditionally fits into two major classes, the so-called “small molecules” (small chemical compounds, some modified short peptides…) and the “biologics” (typically macromolecules such as recombinant proteins, antibodies, siRNAs, long peptides, cells, genes … and vaccines). It is also important to note that gene therapy is different from the other types of therapeutic agents

Fig. Trial Phase

because it is a technique that modifies a person's genes to treat or cure a disease. In this case, the target is a disease-causing gene which has to be modified with a healthy copy of the gene, or the disease causing gene could be inactivated. Thus, beside technical issues, there are a number of ethical questions surrounding gene therapy and genome editing strategies that are not easy to answer.

Further, some therapeutic agents are not acceptable to some parts of the population, as seen during the COVID-19 crisis and vaccine hesitancy. This is often due to misunderstanding of the biological processes and misinformation, resulting in fears, but yet this has to be considered. Also, about 5%–10% of the population are non-responders and have to receive other medications than vaccines. The division into small molecules and biologics is far from being perfect as some therapeutic agents combine a small molecule grafted onto a biologic (e.g., tisotumab vedotin is an antibody-drug conjugate used to treat cervical cancer).

Therapeutic agents can be administrated to patients via different routes, called "routes of administration". Small molecules can in general be administrated orally (the most convenient route for patients), while biologics usually need to be injected. The choice of a route of administration is also governed by the patient's condition, for instance, in acute situations in hospitals, drugs are most often given intravenously. Other critical medical interventions that will not be discussed here are surgery, radiotherapy and psychological support.

TRENDS IN DRUG DISCOVERY AND DEVELOPMENT

⩥ **Artificial Intelligence and Data Analytics**

Research companies are increasingly leveraging big data, AI, and machine learning to automate data processing, enabling quicker solutions to complex problems. AI-driven drug discovery platforms are emerging, predicting new effects and digitizing human cells.

⩥ **Patient-Focused Trials**

Pharmaceutical companies are utilizing applications to gather real-world data, tracking drug safety and efficiency. Testing solutions replicate human organs, running experiments on biosensor-controlled chips to map tissues automatically.

⩥ **Assay Development**

The development of assays is pivotal for new drug development, with companies creating sensors to measure molecular interactions in living cells. This patented technology enables real-time binding visualization, reducing the cost of assay designs.

⩥ **Advanced Manufacturing**

Physical technology, including robotics and augmented reality, is enhancing the clinical manufacturing process. Companies are developing biological coatings for drugs in stable lipids, protecting them from degradation and extending their shelf life.

⩥ **Synthetic Biology**

Synthesizing cells enables safer and quicker drug development. AI is used to produce plant proteins, antibodies, and enzymes for plant-based therapies, advancing genomics-guided drug protection.

⩥ **3D Cell Culture**

The use of 3D modeling provides more accurate results than traditional 2D methods, mimicking cell-to-cell interactions. Pharmaceutical companies are at the forefront of developing 3D cell structure systems, offering higher resolution for improved data in personalized medicine decisions.

Drug Discovery Target and Receptor

A receptor is the specific chemical constituent of the cell with which a drug interacts to produce its pharmacological effects.

⩥ **Receptor:** Any cellular macromolecule that a drug binds to initiate its effects.

⩥ **Drug:** A chemical substance that interacts with a biological system to produce a physiologic effect. All drugs are chemicals but not all chemicals are drugs.

l. Enzyme Inhibition:

Drugs act within the cell by modifying normal biochemical reactions. Enzyme inhibition may be reversible or non-reversible Competitive or non-competitive. Antimetabolites may be used which mimic natural metabolites. Gene functions may be suppressed.

2. Drug-Receptor Interaction:

Drugs act on the cell membrane by physical and/or chemical interactions-usually through specific drug receptor sites known to be located on the membrane. Some receptor sites have been identified with specific parts of proteins and nucleic acids. In most cases, the chemical nature of the receptor site remains obscure.

3. Non-specific Interactions:

Drugs act exclusively by physical means outside of cells. These sites include external surfaces of skin and gastro-intestinal tract. Drugs also act outside of cell membranesby chemical interactions. Neutralization of stomach acid by antacids is a good example.

The binding of a drug to a receptor is determined by the following forces:

1. Hydrogen bonds
2. Ionic bonds
3. Van der Waals forces
4. Covalent bonds.

DRUG DEVELOPMENT CYCLE

There are two broad sections to the drug development cycle the preclinical phase and the clinical phase.

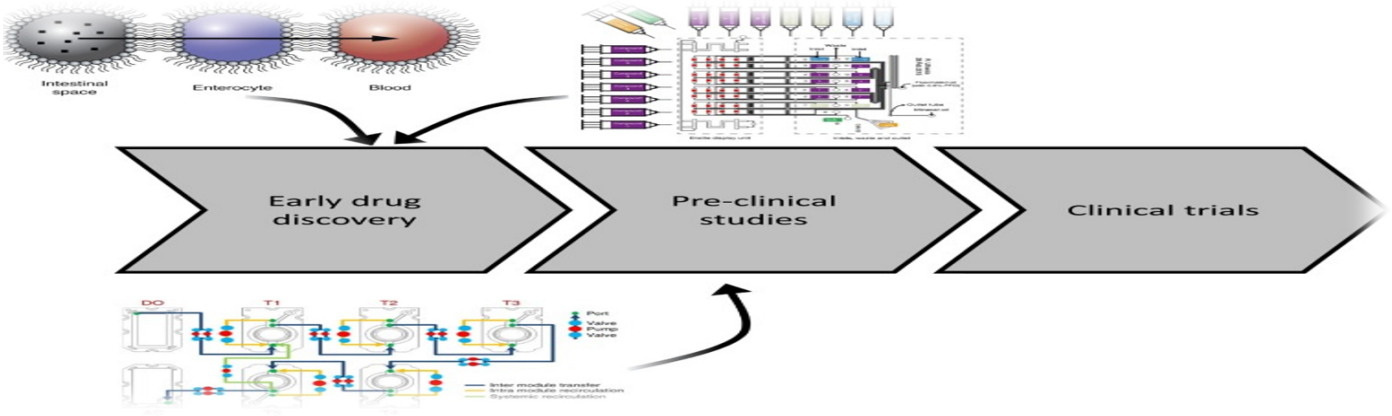

Fig. Drug Development Cycle

PRECLINICAL STUDIES

Once researchers have identified a potential drug via the research and development stages, preclinical testing can occur. For preclinical and clinical testing, agencies worldwide regulate and monitor the industry. For the UK it is the Medicines and Healthcare Products Regulatory Agency, whereas the USA has the Food and Drug Administration.These agencies process Investigational New Drug (IND) applications which, once approved, allow clinical trials to proceed. There are three parts in IND applications: formulation development, pharmacology, and toxicology. Formulation development assesses the best way to prepare a drug in the preclinical phase for its intended clinical use in patients. Factors such as solubility, frequency and mode of administration, stability of the formula, and palatability are all assessed. This takes into consideration where the disease or problem occurs, such as the sinuses or tumors cells.

Pharmacology

The pharmacology stage assesses the safety of a drug as well as its ADME – Absorption; Distribution; Metabolism; and Excretion. ADME is the backbone of pharmacology.

ADME

Absorption concerns the bioavailability of the drug once administered. Before most drugs can achieve their goal, the bloodstream carries them away. The bioavailability of the drug measures the fraction of an administered drug dose that reaches the target system, while also measuring the uptake in the target cells and organs.Once the body has absorbed a drug, the latter distributes from one part of the body to another.Metabolism studies the metabolites produced by the drug's breakdown. It then evaluates whether they are active or harmful, and the breakdown's location in the body.Finally, excretion looks at how the drugs and the metabolites produced exit the body.While ADME is not a regulatory requirement for a first-time, in man (FTIM) study, having conducted it helps improve the quality of the safety information and gives further information to pharmacology and toxicology studies.

Safety

The safety assessment of a drug monitors both pharmacodynamics (PD) and pharmacokinetic (PK) interactions. PD interactions are where the drug administered can affect the actions of another specified drug without affecting its concentration, such as warfarin and antibiotics used in tandem. PK interactions are where the drug administered can affect the actions of another specified drug by affecting its concentration or that of its metabolites, such as the relationship between alcohol and paracetamol.Safety plays a huge part in the preclinical stage of pharmaceutical product development: researchers must test any drugs vying for IND status extensively before allowing human testing.

Researchers can use computer modeling and simulations to an extent; however, they still require animal models to assess safety. This is because they will assess the pharmacodynamics of the drug on a number of the major body systems such as:the cardiovascular and respiratory systems&renal functionality and intestinal transit.

Toxicology inthe Preclinical Phase

Since researchers need to conduct IND tests in animal models, they must conduct studies in two species. This part of the testing is highly regulated. Researchers must use one species that is non-rodent and their use of primates as an animal model is heavily restricted.

The toxicology studies aim to look at the effects of longer-term drug exposure on the body, including repeat dose studies. Pharmaceutical companies deliberately conduct studies over longer time periods than a human would take the drug for, with the duration of the study dictated by the anticipated exposure time that a human would face. For example, if the drug regime calls for daily doses for a seven-day period in humans, animal models undergo the treatment for four weeks. Similarly, a 30-day repeated dose in humans would call for a three-month trial in both animal species.

During these studies, researchers assess parameters such as food and water consumption, body weight, hematology and urine analysis. These aim to monitor for any adverse effects that could arise as a result of taking the drug. Researchers will also monitor immune responses, such as infection occurrences, tumor incidences and histological changes in the immune system.60% of potential drugs fail in the preclinical phase of pharmaceutical product development.

CLINICAL STUDIES

Phases of Clinical Trials:

Preclinical studies: Before starting of clinical trials of a drug, the pharmaceutical companies perform an preclinical studies which consist of in vitro (animal), in vivo (cell culture) experiments by using wide range of doses study to obtain primary efficacy, toxicity and pharmacokinetic information. Such experiments helps the pharmaceutical companies to decide whether the drug have scientific merit or not. In addition, decision on whether it has been required for further development as an investigational new drug.

Clinical trials testing new treatments are divided into different stages, called phases. The earliest phase trials may look at whether a drug is safe or the side effects it causes. Later phase trials aim to test whether a new treatment is better than existing treatments.

There are 3 main phases of clinical trials – phases 1 to 3. Phase 1 trials are the earliest phase trials and phases 3 are later phase trials. Some trials have an earlier stage called phase 0, and there are some phase 4

Fig. Clinical Trial various phases

trials done after a drug has been licensed. Some trials are randomized. This means the people taking part are put into one of the treatment groups at random. Doing this means the results are more reliable.

Phase 0 trials:

The earliest trials of drugs in people are usually phase 1 trials. But your doctor might ask if you would like to join a phase 0 study. These studies aim to find out if a drug behaves in the way researchers expect it to from their laboratory studies. Phase 0 studies usually only involve a small number of people and they only have a very small dose of a drug. The dose of the drug is too small to treat your cancer, but you are also less likely to have side effects.

Phase 0 trials aim to find out things such as:

•whether the drug reaches the cancer cells
•what happens to the drug in the body
•how cancer cells in the body respond to the drug

You might have extra scans and give extra samples of blood and cancer tissue (biopsies) to help the researchers work out what is happening.

Phase 1 trial:

They are usually small trials, recruiting only a few patients. The trial may be open to people with any type of advanced cancer, usually those who have already had all other available treatments.

Phase 1 trials aim to find out:

•how much of the drug is safe to give
•what the side effects are
•what happens to the drug in the body

Patients are recruited very slowly onto phase 1 trials. So even though they don't recruit many people, they can take a long time to complete. In a phase 1 trial you may have lots of blood tests because the researchers look at how your body copes with and gets rid of the drug. They carefully record any side affects you may have and when you have them. The main aim of phase 1 trials is to find out about doses and side effects. They need to do this first, before testing the potential new treatment to see if it works. Some people taking part may benefit from the new treatment, but many won't.

Phase 2 trials:

Phase 2 is sometimes written as phase II. Not all treatments tested in a phase 1 trial make it to a phase 2 trial. These trials can be for people who all have the same type of cancer, or for people who have different types of cancer.

Phase 2 trials aim to find out:

- if the new treatment works well enough to be tested in a larger phase 3 trial
- More about side effects and how to manage them
- More about the best dose to give

These treatments have been tested in phase 1 trials, but you may still have side effects that the doctors don't know about. Treatments can affect people in different ways. Some people taking part may benefit from the new treatment, but some won't. Phase 2 trials are usually larger than phase 1. There may be up to 100 or so people taking part. Sometimes in a phase 2 trial, a new treatment is compared with another treatment already in use, or with a dummy drug (placebo). Some phase 2 trials are randomized. This means the researchers put the people taking part into treatment groups at random.

Phase 3 trials:

These trials compare new treatments with the best currently available treatment (the standard treatment).

Phase 3 trials aim to find out:

- Which treatment works better for a particular type of disease
- More about the side effects
- How the treatment affects people's quality of life

They may compare standard treatment with:

- A completely new treatment
- Different doses of the same treatment
- Having the same treatment more, or less, often
- A new way of giving a standard treatment (radiotherapy for example)
- Phase 3 trials usually involve many more patients than phase 1 or 2. This is because differences in success rates may be small. So, the trial needs many patients to be able to show the difference. Sometimes phase 3 trials involve thousands of people in many different hospitals and even different countries. Most phase 3 trials are randomized. This means the people taking part are put into treatment groups at random. See our information about randomized trials.

Phase 4 trials:

Phase 4 is sometimes written as phase IV. These trials are done after a drug has been shown to work and has been licensed. Phase 4 trials aim to find out:

- More about the side effects including the rarer side effects and safety of the drug
- What the long term risks and benefits are
- How well the drug works when it's used more widely for people not included in the phase 3 trial

Phase IV, also referred to as "Post marketing surveillance" (Pharmacovigilance), and includes the technical support of the drug after the selling permission of the drug is achieved4-5. The Phase IV studies can be performed with the help of regulatory authority or by sponsoring company for finding a new market of the drug. Such trails have been designed to find out if any long term adverse effect over a much large population of patients for a longer period of time, that were not possible during Phase II and phase III trials, has been noted. However, the whole process of the drug from the lab to this point takes about 12-18 years approximately

Phase 5 trials:

New term used in the literature, is also termed as "translational research" to refer the effectiveness and community based research studies. It is used to find the interrogation of a new clinical treatment into a large number of public health practices. Generally, the Phase V trials have been considered as the "field research" and it is particularly designed to test generalization of the mechanism to a large sample.

CONCULSION

Drug discovery and development is a long and difficult endeavor; all novel ideas and strategies that can improve the process are valuable to explore. It is interesting to note that despite the steady increase in research and development expenditure, and major scientific advances in proteomics and genomics, the discovery of new drugs either seems to be drying-up some years or to remain essentially stable.This situation has various origins (e.g., many diseases with no treatment are extremely difficult to study), while, certainly, industry scientists would benefit from greater exposure to new ideas from public research and public researchers would benefit from the private sector to move beyond exploration of molecular mechanisms towards the end goal of efficient development of candidate therapeutic agents. Along these lines, some countries like the United States and United Kingdom have been working extensively at improving academic drug discovery

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