AI in Drug Discovery and Development

Prof. Rajnish Kumar
Dept. of Pharmaceutical Engineering and Technology
IIT-(BHU), Varanasi

Week-01
Lecture-01

Welcome to the course AI in Drug Discovery. So, today we will talk about drug discovery and development. So, in today's lecture, the learning objectives are that by the end of this lecture you will be able to outline the key stages of drug discovery and development, understand the historical evolution of drug discovery, identify the roles of key stakeholders including pharmaceutical companies, regulatory agencies and academic institutions in drug discovery and also assess the investment, risk and challenges in bringing a drug to the market. So, every day we are using drugs in the form of medicine. So, a drug by definition is any substance other than food or nutrient which is used to prevent, diagnose, treat or alleviate the symptoms of a disease or an ailment. So, it can be a prophylactic in nature where the treatment that prevents disease or slows its progression.

For example, folic acid is used for prevention of anemia or it can be therapeutic in nature where the treatment helps with the disease or condition like in the case of cancer where we use chemotherapy to treat it. Or it can also be symptomatic in nature, where it is just reducing the symptoms, but does not change the underlying disease. For example, we use paracetamol to cure the fever, which we have due to any infection. Or the drug can be disease modifying as well.

So, for example, the drug lufalonamide, which is an immunosuppressive agent used for rheumatoid arthritis. So, the drugs can be from natural or synthetic origin. For example, we have paracetamol, which is coming from synthetic origin, and we have the drug morphine, which is obtained from the plant, Papaver somniferum, which comes from a natural origin. So overall, drug discovery and development can be divided into two parts. One is called as drug discovery, which is the process of identifying new chemical entities or biological molecules that have the potential to treat or cure disease.

And the later part is drug development, which involves taking this potential treatment through rigorous testing and regulatory approvals to finally make it available in the clinic for the patient. So, the process is crucial for advancing medical treatment, improving patient outcomes and addressing unmet medical needs. So, as I said like the drug discovery and development is divided into two parts, one is the drug discovery phase, another one is the development phase. So, the discovery phase starts with identification of the targets and their validation, where we select a particular biological target corresponding to a disease

and followed by identifying hit compounds by doing compound screening. So, we do identify hit compounds.

We use either high throughput screening or virtual screening in that case and followed by lead optimization. So, we optimize those hit compounds into leads which have the optimal properties. So, these lead compounds are then further developed into, you know, preclinical drug candidates where they go through early toxicology studies, proof of concept studies to establish their potency, efficacy and also pharmacokinetic screening in animal models. So, this whole part is called as drug discovery where the success rate is very low just 2 to 5 percent and it is highly costly which takes around half a billion US dollar and it takes a lot of time around 3 to 5 years on an average. So, once the discovery part is over so, then the molecule which is now called as the drug candidate, it moves to the development phase where the clinical trials are undertaken and then the molecules are being tested in humans.

So, through several clinical trials like phase 1, phase 2, phase 3. And once we get good results from clinical trials, so then after the regulatory approval from regulatory bodies, so that the drug sees the market and then that is available in the clinic for the treatment of patients. So, the development part also is very, you know, time intensive. So, it takes around four to six years on an average. And it's again costly, takes around half a billion US dollar and the success rate is very low as well.

So, if you look at the historical context, like how drugs were discovered in the early age, so there have been examples of, you know, use of different substances as drugs. For example, in 7000 to 5500 BC, it was found that people were using betel nuts and it was found in the spirit caves of north-western Thailand and it is considered as a mild psychoactive agent. Likewise, around 7000 to 5000 BC, so the use of hallucinogenic mushroom was also implicated by Saharan cave drawings. Likewise, in 2680 BC, so lime containing betel nut shells found in Duyong cave of the Philippines and it is highly prevalent in use in India at present as well. And also, as we know that the use of alcohol for recreational and medicinal purpose is a very well known.

So, there are early documented evidences as well, like the treatise of medical diagnosis and prognosis, which document medical methods and prescriptions on stone tablets by Mesopotamians in around 1700 BC. And then Ebers Papyrus, it is by the ancient Egyptians, which contains several hundred prescriptions for the treatment of disease or symptomatic relief in around 1550 BC. And Charaka Samhita, which is one of the foundational texts of Ayurveda, written by Acharya Charaka, which focuses on health preservation, disease prevention and holistic healing. So, the basic principles of prehistoric drug discovery were that it was exclusively depending upon plants or plant derived mixtures or plant extracts. So, the medications were identified using empirical observations of the presence or absence

of symptoms in patients rather than an understanding of the disease or condition afflicting the patients.

So, all of the efforts were made in the absence of the vast majority of fundamental knowledge required to understand even the basic principles of disease progression. So, one of the examples is discovery of quinine where the quinine was discovered by Agostino Salumbarino. So, he observed that Quechua people. So, these were the people from a specific tribe. So, they were chewing the bark from the cinchona tree whenever they were getting shivering and fevers.

So, what he did was he thought that bark can contain something which is relieving the fever. So, he sent those samples of that bark to Rome for evaluation as a treatment for malaria. And then he identified that it is having anti-malarial activity. So, therefore, the Quechua people became the source of first successful anti-malarial agent, a drug that was a first-line treatment for malaria infection until 2006. If you look at the big picture of drug discovery, so drug discovery is a driver of medical innovation.

Everyday researchers are innovating novel drugs for the treatment of various diseases. So, it has global impact as well because it has improved the life expectancy as well as quality of life and it is also leading to economic benefits. So, it works at the intersection of science, medicine and business and it is also a continuous cycle of innovation addressing evolving health challenges. So, the key objectives of drug discovery and development are to develop safe and effective treatments for diseases, to address the unmet medical need and the rare diseases as well and to improve the existing therapies. For example, reducing the side effects or improving the efficacy of the existing drugs as well as enhancing patient quality of life and treatment outcomes.

So, if you look at the scope of drug discovery, so there are different types of drugs being used in the clinics. So, for example, there are small molecule drugs which are small molecules having molecular weight less than 500 generally. And then there are biologicals which are large and complex molecules such as monoclonal antibodies or vaccines. And then there are advanced therapeutics like gene therapies where people try to modify or replace the faulty gene. And then it encompasses the wide therapeutic areas from cardiovascular diseases to cancer to rare genetic disorders.

So, the drug development timeline is a very important aspect of drug discovery and development. So, if you look at the timeline, so the average time taken by a drug to reach from the target identification to the clinical trial or to reach to the clinic. So, it takes around 10 to 15 years actually. And then the key phases are like basic research, discovery, clinical studies, clinical trials, regulatory review and post-market surveillance. And the emphasis

is on the long-term nature and complexity of the process.

So, if we talk about the investment and risk, so the average cost to develop a new drug is around 1 to 2 billion US dollars. Again, it depends on the nature of the disease. And then there is a very high failure rate because only about one in 10,000 compounds, they make it to the market. And then the risk factors lie in scientific uncertainties, regulatory hurdles and market competitions. So, we will talk about these issues later during the course.

And then there is an importance of robust pipelines and diverse portfolios for pharmaceutical companies as well. So, these are different stakeholders in drug discovery. So, we have the pharmaceutical companies who are involved in developing those drugs. We have the biotechnology firms. We have the advocacy groups.

We have the patients. We have the government agencies. We have the academic institutions. So overall, they play a very important role overall process of drug discovery and development. So, if we talk about the role of academia in drug discovery, so the academia plays a very important role in drug discovery and development. So, it can contribute to the fundamental research in disease mechanism and potential targets.

It can also help in development of new technologies and methodologies for synthesizing those drugs maybe and it also trains the future scientists and researchers which originally contribute to the discovery of the drugs in the research. So, it also helps in training of future scientists and researchers as well which further contributes to the drug discovery and development. And then the academia, they collaborate with industry through technology transfer and joint research projects as well. So, one of the successful examples of role of academia in drug discovery and development is the discovery of candocuronium iodide, which is originally known as chandonium iodide or HS310, which is a neuromuscular blocking agent discovered by the team of Professor Harkishan Singh at the University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India. So, the pharmaceutical industry also plays a very important role where it helps in the large-scale drug discovery and development programs.

They have the expertise in translating basic research into therapies. They have all the resources for extensive clinical trials and regulatory processes. And then they have resources for manufacturing and distribution of approved drugs as well. And, they continuously do investment in R&D for future treatments. The regulatory agencies also play very important role in ensuring safety and efficacy of new drugs.

So, we have FDA, EMA or CDSCO in case of India. So, which regulates the process of drug discovery and development by establishing guidelines for drug development and

clinical trials and by reviewing and approving new drug applications. So, the regulatory agencies also play an important role in post-market surveillance for long-term safety of the approved drugs and then they balance the need for thorough evaluation with timely access to new treatments. So, there are some ethical considerations as well that we have to ensure the patient safety in clinical trials and we need to get an informed consent and protection of vulnerable population. And there should be equitable access to new medicines and then the pricing and affordability of drugs need to be taken care of.

And then there should be a balancing profit motives with public health needs and ethical use of animals in preclinical research as well. So, the process of drug discovery and development is highly interdisciplinary in nature, where different fields such as chemistry, biology, pharmacology, medicine, data science, they come together and work for a single aim to discover a drug to treat the disease. So, where the chemistry people they help in designing and synthesizing new compounds, the biology team helps in understanding the disease mechanism and drug targets, the pharmacology team studies the drug effects and mechanism of action and then the medicine team helps in translating those discoveries into clinical application and the data science team they analyze large data sets and predict the outcomes. So, ultimately overall if we see that the interdisciplinary collaboration is the key to success of drug discovery and development. So, there have been several technological advancements.

So, like there have been developments in genomics and proteomics, which nowadays helps in identifying new targets and developing personalized treatments. And there has been developments in high throughput screening as well, where you can test thousands of compounds rapidly in a very short time. The structure-based drug design methods have also matured a lot, where you can use the 3D structures of the protein structures to design targeted therapies. And the AI and machine learning is helping a lot in predicting drug properties and optimizing molecules. And then the organ on a chip technology, it helps in mimicking human physiology for better preclinical testing.

So, now nowadays there are several methods which are available where you can evaluate your molecules in a lab on chip technology instead of testing it on animals. So, there are several success stories as well. For example, the discovery of drugs for the treatment of HIV and AIDS, which was once considered a fatal disease, but now it is a manageable condition. And then there is the discovery of imatinib which is a targeted therapy which revolutionized chronic myeloid leukemia treatment. And then there are drugs for the treatment of hepatitis C and CAR T cell therapy as well.

So, these are some of the anti-cancer drugs which have been discovered. For example, the Paclitaxel, Vinblastine, Doxorubicin, Topotecan, Imatinib and all. So, these are highly

successful drugs for the treatment of cancer. And these have been possible only because of the hard work and efforts of researchers working in the field of drug discovery and development. So, we have to learn from the failures as well.

So, here we will talk about the thalidomide story. So, which was one of the potential drugs used to treat the morning sickness during pregnancy. Between 1954 to 1956, the clinical safety of the thalidomide was established for its use to treat morning sickness in pregnancy. And animal studies did not indicate any kind of acute toxicity. But in 1960, so peripheral neuropathy was indicated after long term use and later on more than 10,000 children were born with severe birth defects linked to thalidomide and those were called as thalidomide babies.

So, later on in 1962 it was withdrawn from the market. So, then the regulatory standards for safety and efficacy testing of new drug candidates were significantly improved. And also, the theories on protection of unborn babies by placenta was revised. Additionally, the importance of drug chirality was brought in drug discovery and development since the S isomer was the culprit and the chiral stability became a new checkpoint for drug discovery and development. So, if we summarize it, so the drug discovery is a systematic multi-stage process that ensures the development of safe and effective treatments and the journey from initial discovery to market approval involves rigorous testing through preclinical and clinical trials And there are various stakeholders which contribute to the process, including the pharmaceutical industry, regulatory authorities and the researchers.

And there are emerging technologies like AI-driven drug design and precision medicines, which are revolutionizing drug discovery. And then the ethical considerations remain crucial in ensuring patient safety, accessibility and regulatory compliance. I have this open question for all of you. How might drug discovery priorities differ between developed and developing countries? What ethical considerations arise from these differences? So, you can also go through these references for knowing more about drug discovery and development. And with all that, thank you so much and see you again in the next session.