Advances in Drug Development Process using AI

Dr. Seema Kohli
HOD, Pharmacy
K.N.Polytechnic College,
Jabalpur, (M.P.), India
seemankohli@gmail.com

Dr. Ankita Alice Singh
Faculty, Pharmacy
K.N.Polytechnic College,
Jabalpur, (M.P.), India

Dr. Kaminee Sahu
Professor, Pharmacy
Gyan Ganaga Instt. Of Science and Technology
Jabalpur, (M.P.), India

Dr. B.K.Jain
Faculty, Pharmacy
K.N.Polytechnic College,
Jabalpur, (M.P.), India

Abstract

Drug discovery and development is essentially concerned with newfangled chemical moiety with biological activity. It works on enhancing the properties of drugs used in the treatment of different medical conditions. The development and launching of a new drug is a highly time consuming, tedious and expensive process. In order to speed up research and estimate the risk and cost of clinical trials, Artificial Intelligence(AI) learning tools and techniques are used throughout all stages of drug development. Through diverse applications like QSAR analysis, hit discoveries, and de novo drug designs, AI approaches enhance decision-making in the pharmaceutical industry to retrieve correct results. This chapter focuses on the various aspects of drug discovery using traditional approaches and the artificial intelligence based digital techniques.

Key words **:** Artificial Intelligence **,** Drug Discovery **,** Machine Learning**,** Drug Target, Drug Lead

I. Introduction

Drug discovery and development is essentially concerned with newfangled chemical moiety with biological activity. It works on enhancing the properties of drugs used in the treatment of different medical conditions. The development and launching of a new drug is a highly time consuming, tedious and expensive process.

Drug discovery leading to strong and doable lead candidate always remained exigent assignment for scientists. In fact experts accomplish the task by transforming the screening hit compound to a suitable drug candidate. The journey of new drug to the market is considerably long and takes about 10-15 years of investigation period. Therefore, the new approaches are obligatory to be developed not only to expedite the process but also to ensure the launch of safer and effective drug [1].

II. Conventional Approach to Drug discovery

Classically, the drug discovery involves under mentioned defined stages:

- Identification of cause of Disease and Search for target site
- Search and Optimisation of active compound i.e. the Drug Lead
- Testing of Drug in Animals (pre-clinical phase) .
- Clinical Trials
- Approval of New Drug by Competent authority and availability in market.

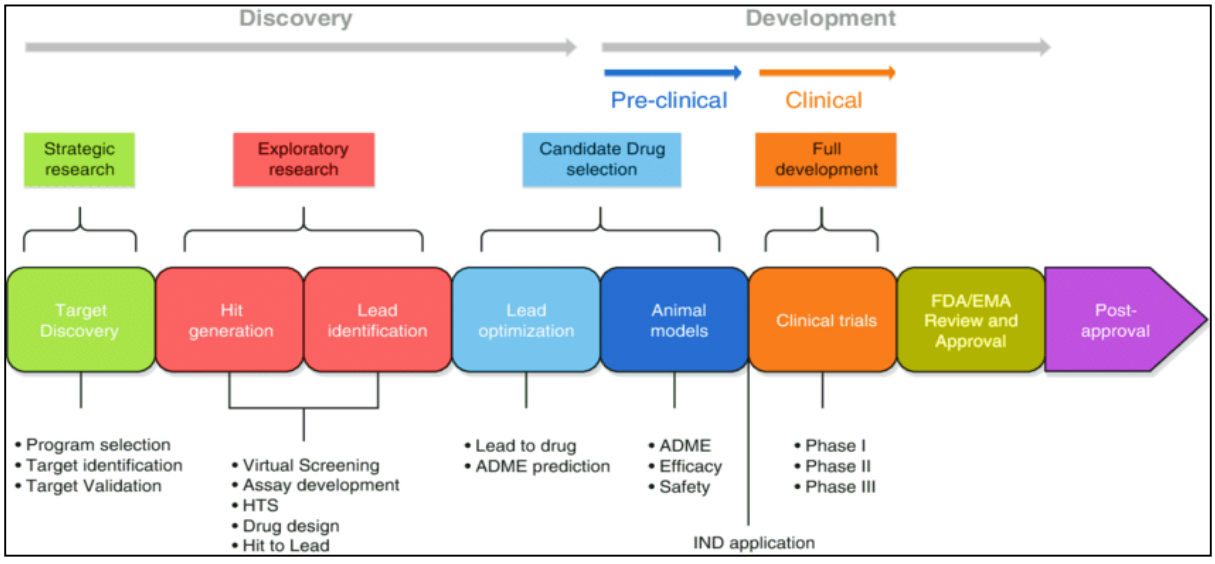

Figure 1: Drug Discovery Process

A. Step I

Typically, researchers discover new drugs through:

- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments that have unanticipated effects.
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.

Once researchers identify a promising compound for development, they conduct experiments to gather information on:

- How it is absorbed, distributed, metabolized, and excreted.
- Its potential benefits and mechanisms of action.
- The best dosage.
- The best way to give the drug (such as by mouth or injection).
- Side effects or adverse events that can often be referred to as toxicity.
- How it affects different groups of people (such as by gender, race, or ethnicity) differently.
- How it interacts with other drugs and treatments.
- Its effectiveness as compared with similar drugs.

Target Discovery

- During the first phase, known as target discovery, *in vitro* research is performed to identify targets involved in specific diseases. A target is usually a molecule integral to gene regulation or intracellular signaling, such as a nucleic acid sequence or protein. In order to decide on which target to focus research efforts, one needs to ensure that the molecule is "druggable" — that its activity can be modulated by an exogenous compound.

Target Validation

- After selecting a potential target, researchers must demonstrate that it is involved in the progression of a given disease and that its activity can be regulated. Conducting careful and precise target validation experiments is essential for the success of **drug development** in the following stages.

Lead Compound Identification

- Lead compound identification is the process of identifying or creating a compound that can interact with the target previously selected. Researchers can conduct screening experiments to identify possible naturally-occurring compounds that can be re-purposed as drugs. Alternatively, synthetic compounds can be designed that will both target the predicted target while not interfering with other cellular processes. In addition to testing the mechanism of action of the drug, initial safety tests are conducted in cell culture. Both the pharmacokinetics and pharmacodynamics of the drug are also tested — how it is metabolized and how it affects various bodily functions, respectively.

Lead Optimization

- Once a compound (or compounds) have been identified, they need to be optimized for efficacy and safety. The design of synthetic molecules can be altered to prevent off-target binding, making them less likely to interact with molecules other than the target. Additionally, the optimal dosage and introduction route (oral, injection) is tested on two- and three-dimensional cell culture platforms.

  This stage also includes safety testing prior to introduction into multiple *in vivo* animal models in the following preclinical development stage. Animal models such as mice and rats can be used at this stage, however some tests for safety are first conducted *in vitro*.

  One specific example of a three-dimensional platform is a scaffold developed for the testing of new glaucoma drugs (Torrejon, KY, 2013). Glaucoma can result from increased intraocular pressure in the eye, which is directly related to the outflow of aqueous humor through a structure called the trabecular

meshwork. The scaffold developed is a three-dimensional trabecular meshwork which effectively mimics the microenvironment around the eye. By screening drugs first in this 3D *in vitro* setting, animal models used in the next stage will have better chances of encountering a safe and effective drug.

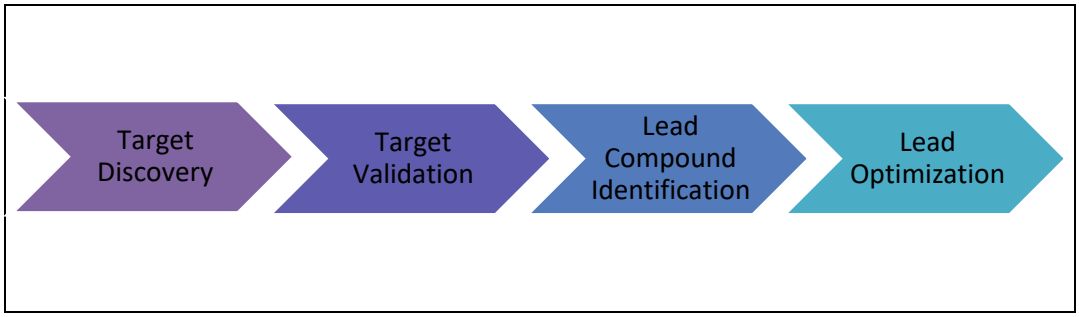

Figure 2: Steps in Stage I of Drug Discovery

B. Stage II

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are:

- In Vitro
- In Vivo

FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies. . These regulations set the minimum basic requirements for:

- study conduct
- personnel
- facilities
- equipment
- written protocols
- operating procedures
- study reports
- and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people.

Advancing to Clinical Trials

Investigational New Drug (IND) Application
Prior to beginning clinical trials, an Investigational New Drug (IND) application must be submitted to the FDA. This document must include:

- Animal study data and toxicity
- Manufacturing information
- Clinical protocols for the proposed human trials
- Data from any prior human research
- Information about the principal investigator(s)

The FDA then conducts an extensive review of the IND, and, after thirty days, can respond to in one of two ways:

1. Approval of the IND and commencement of clinical trials
2. Temporary hold until additional information is obtained, or a stop of the investigation entirely

C. Stage III - Clinical Trials

Figure 3: Phases in Clinical Trials

- **Phase I Clinical Trials**

During phase I of clinical trials, the new drug is tested on 100 or less healthy patients to determine the relative safety of the medication.

This phase also includes carcinogenicity testing on mouse animal models, specifically the **Tg rasH2 mouse**, which is used to predict the carcinogenic potential of chemicals. This mouse model carries the human c-Ha-ras oncogene in addition the endogenous mouse Ha-ras oncogene. The presence of the human copy of this gene makes the model highly susceptible to developing tumor after exposure to compounds that cause cancer in humans. This model had reduced the time associated with carcinogenicity testing from two years down to six months.

- **Phase II Clinical Trials**

During phase II, the amount of patients increases to a group of 100-500 and the drug's effectiveness is studied. These patients have the disease that the new drug is attempting to treat. Adverse events, side effects, and efficacy are all tested in this phase.

Other questions that are asked are the optimal dosage, frequency of intake, and the effect it has on the condition in question.

- **Phase III Clinical Trials**

In Phase III trials, researchers study the drug a group of about 1,000-5,000 patients in order to generate statistically significant data. Only 12% of drugs make it through this stage, as it is key to determining the overall safety and efficacy of the new medication. If a drug is able to pass through this stage, data obtained from the larger group of patients provides the basis for the future labeling of the prescription.

D. Stage IV

- **FDA Review and Approval**

After clinical trials have succeeded, a New Drug Application (NDA) is submitted to the FDA for review and potential approval. The purpose of this document is to demonstrate the clinical trials proved the safety and efficacy of the drug, and that it is qualified to go to market. Lots of data is required for this, including information about all phases and studies, clinical results, safety precautions, and potential interactions with other medications. The review process can take anywhere from six to ten months.

If a drug is approved at this point, the labeling processes begins, which is the development of prescribing information that accompanies all prescription medications in the US.

E. Stage V

- **FDA Post-Market Drug Safety Monitoring**

Even though clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval. Despite the rigorous steps in the process of drug development, limitations exist. Therefore, the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime in the marketplace. FDA reviews reports of problems with prescription and over-the-counter drugs, and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues [2].

III. Challenges in Traditional Drug Discovery Process

- Drug development is a lengthy, complex, and costly process, entrenched with a high degree of uncertainty that a drug will actually succeed.
- The unknown pathophysiology for many nervous system disorders makes target identification challenging.
- Animal models often cannot recapitulate an entire disorder or disease.
- Challenges related to heterogeneity of the patient population might be alleviated with increased clinical phenotyping and endo-typing.
- Greater emphasis on human data might lead to improved target identification and validation.
- There is a lack of validated diagnostic and therapeutic biomarkers to objectively detect and measure biological states.
- Unfamiliarity with current regulatory processes for investigational new drug (IND) applications can be resolved through pre-IND meetings.[3][4]

IV. Novel approaches in Drug Development using AI

In order to speed up research and estimate the risk and cost of clinical trials, machine learning tools and techniques are used throughout all stages of drug development. Through diverse applications like QSAR analysis, hit discoveries, and de novo drug designs, machine learning approaches enhance decision-making in the pharmaceutical industry to retrieve correct results. Machine learning needs to be modified well in the utilization of any kind of information i.e., initially, a particular model must be characterized along with parameters. The medical information was being mined and estimated accurately by using some 'omics' and 'smart' automation tools. Enlarging these techniques into the biological field gives more opportunities as well as challenges in the pharmaceutical industry.

In computer science, machine learning (ML) is an area of artificial intelligence (AI). A machine learning algorithm in this context refers to any computing technique that uses the outcomes of past actions, decisions, or

observations to enhance forecasts or future decision-making. Nowadays, ML methods are widely used in the pharmaceutical industry**.**

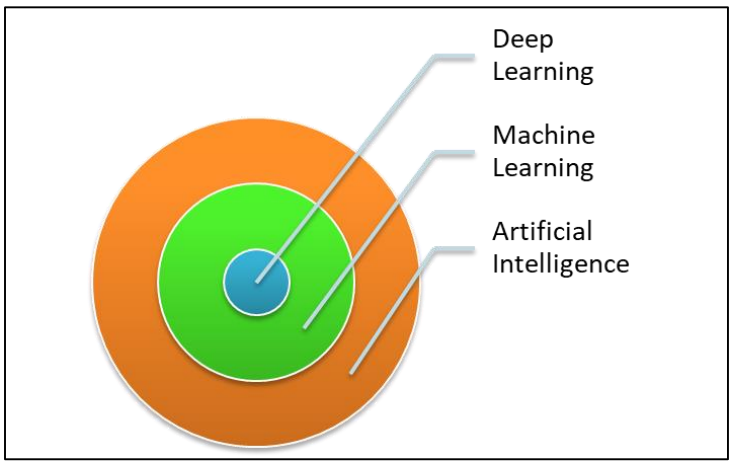

Figure 4: Relatioship betwwn AI, ML and DL

In drug discovery, computational intelligence provides various techniques for analyzing, learning and furthermore clarifies how such pharmaceutical was identified with AI for finding numerous medications in a programmed and integrated format. Therefore, many pharmaceutical industries have shown greater enthusiasm for contributing to technologies, resources for retrieving accurate results in drug discovery.

V. AI potential to transform the drug development process

- Pharmaceutical companies are routinely faced with drug development timelines of about 15 years, costs in excess of $1 billion, and a minute rate of success.
- Many disease conditions cannot be successfully addressed through the traditional drug development process.
- It's estimated that 1 in 10 small molecule projects become candidates for clinical trials and only about 1 in 10 of those compounds will then pass successfully through clinical trials.
- Barriers include inability to devise a molecule that selectively drugs the desired target or absence of sufficient financial incentives based on size of addressable market.
- AI has the potential to transform the drug development process making it both more efficient and more effective, thus benefiting all parties involved from the companies developing new drugs to the patients in desperate need of viable treatments.

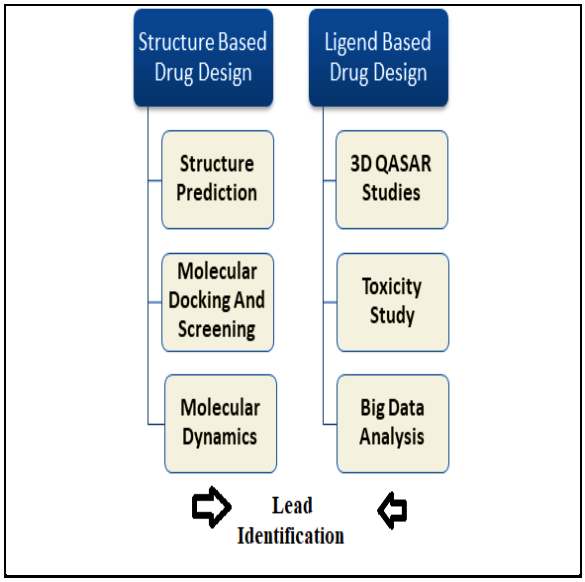

Figure 5: Recent Trends In Drug Discovery

Machine learning tasks are grouped l broadly into three categories.

- The first one is supervised learning, in which the goal is to predict the label of new observations given a large database of labelled examples. Several supervised learning algorithms have been applied in a biological context, such as Support Vector Machines [32] or (Deep) Neural Networks [33].
- The second task is unsupervised learning, and it aims at detecting underlying relationships or patterns in unlabeled data.
- The third type of task is sequential learning, where algorithms rely on trial-and error, and iteratively use external observations in order to find the best.[5]

VI. AI use in drug discovery

Traditional drug discovery methods are target-driven, i.e., a known target is used to screen for small molecules that either interact with it or affect its function in cells.

- These approaches work well for easily druggable targets that have a well-defined structure and whose interactions inside the cell are understood in detail.
- However, these methods are extremely limited due to the complex nature of cellular interactions as well as limited knowledge of intricate cellular pathways.

AI can overcome these challenges by identifying novel interactions and inferring functional importance of different components of a cellular pathway.

- AI utilizes complex algorithms and machine learning to extract meaningful information from a large dataset, e.g., a dataset of RNA sequencing can be used to identify genes whose expression correlates with a given cellular condition.
- AI can also be used to identify compounds that could bind to ‘undruggable targets’, i.e., proteins whose structures are not defined. Through iterative simulations of interactions of different compounds with small pieces of a protein, a predictive set of compounds can be easily identified in a relatively small amount of time.

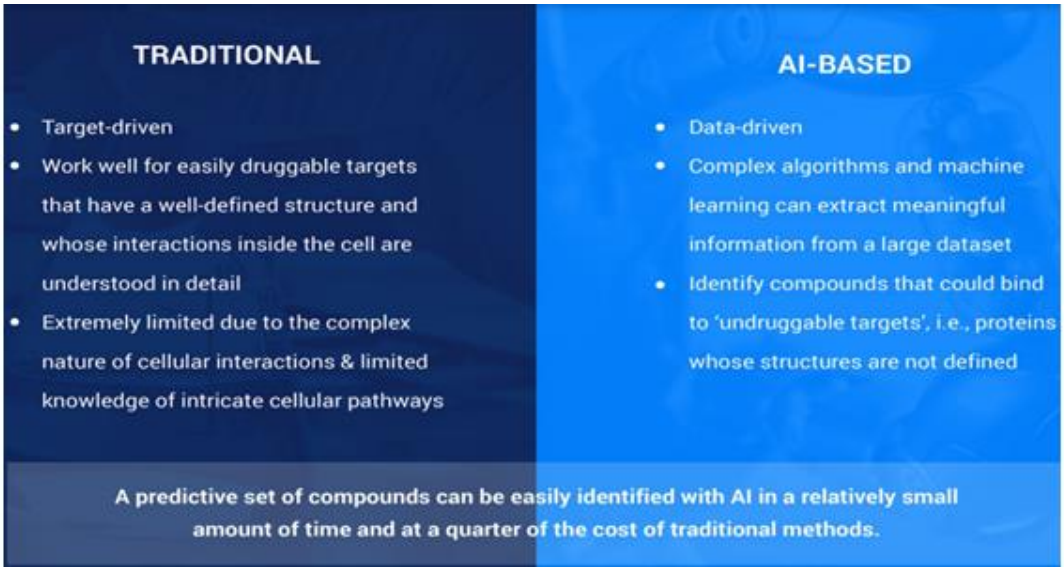

Figure 6: Traditional Vs AI based Drug Development Process

VII. Benefits of applying AI to drug discovery

The application of AI to drug discovery has the potential to revolutionize the current time scale and scope of drug discovery.

- AI does not rely on predetermined targets for drug discovery. Therefore, subjective bias and existing knowledge is not a factor in this drug development process.
- AI utilizes the latest advances in biology and computing to develop state-of-the-art algorithms for drug discovery. With the rapid increase in processing power and reduction in processing cost, AI has the potential to level the playing field in drug development.
- AI has a higher predictive power to define meaningful interactions in a drug screen.
- Therefore, the potential for false positives can be reduced by carefully designing the parameters of the assay in question.
- Most importantly, AI has the potential to move drug screening from the bench to a virtual lab, where results of a screen can be obtained with greater speed and promising targets can be shortlisted without the need for extensive experimental input and manpower hours.

VIII. Drawbacks of applying AI to drug discovery

- As is the case with any advance that brings a paradigm shift in our understanding of an existing technology, AI still cannot replace a human scientist entirely in the process of drug discovery.
- AI predictions are as good as the algorithms used to investigate a dataset.
- The algorithm should clearly lay out the criteria that should be used to parse out meaningful information when the results are in the 'gray zone' of interpretation.
- AI can suffer from algorithm bias, where the creators' own bias manifests itself in the way information is processed to generate predictions.
- Therefore, the process is not entirely objective.

- While the cost of supercomputing and high-throughput screening has decreased appreciably over the past decade, establishing these pipelines still requires significant investment.
- Ultimately, predictions made by a computer have to be verified by a scientist to make sure they are valid.[6][7]

IX. AI based Tools Employed in Drug Discovery

The various tools used AI drug discovery are listed below [5]

Table 1 Examples of AI Tools

Tools	Details	Website URL
Neural graph fingerprint	**To evaluate properties of novel molecules**	**https://github.com/HIPS/neural-fingerprint**
DeepChem	**Used to find out suitable drug candidate**	**https://github.com/deepchem/deepchem**
DeepTox	**Prediction of drug toxicity**	**www.bioinf.jku.at/research/DeepTox**
Hit Dexter	**To identify molecules that may react to biochemical tests.**	**http://hitdexter2.zbh.uni-hamburg.de**
DeepNeuralNetQSAR	**Detection of the molecular activity of compounds**	**https://github.com/Merck/DeepNeuralNet-QSAR**
ORGANIC	**Helps to create molecules with desired properties**	**https://github.com/aspuru-guzik-group/ORGANIC**
PotentialNet	**Employs Neural networks to envisage binding affinity of ligands**	**https://pubs.acs.org/doi/full/10.1021/acscentsci.8b00507**
Chemputer	**Assist in procedure for chemical synthesis**	**https://zenodo.org/record/1481731**
DeltaVina	**To know drug–ligand binding affinity**	**https://github.com/chengwang88/deltavina**

X. Success Stories in AI Driven Drug Discovery

AI has revolutionized the drug discovery process. The AI based tool uses technology that copies the human intelligence in solving complex clinical problems. Here are certain examples that denotes the milestones in drug discovery process. [9]

- In 2020, the company Exscientia proclaimed the discovery of first AI drug molecule to be submitted for human clinical trials.
- In July 2021, AlphaFold, an artificial intelligence (AI) system developed by DeepMind, predicted the structure of 330,000 proteins. That's more than 20 times the number of proteins in the entire human genome.
- In February 2022 Insilico Medicine named company announced the initiation of Phase I clinical studies for the world's first AI-based molecule based on a novel AI-discovered target in comparatively less time and cost than traditional preclinical programs.
- In January 2023, AbSci company became the first "to create and validate *de novo* antibodies *in silico*" using AI technology.
- FDA granted its first Orphan Drug Designation in February 2023 to a drug discovered and designed by using AI approaches that was then initiated for Phase II Clinical trials.

XI. Conclusion

The path of drug discovery from a small molecule ligand to a clinically useful drug is a long and strenuous process. The presented basic concept and application of artificial intelligence in drug design and development will facilitate this process. In particular, machine learning and deep learning, which have shown great utility in many areas of computer-aided drug development, such as new drug development, QSAR analysis and chemical state imaging. Artificial intelligence-integrated drug discovery and development has accelerated the growth of the pharmaceutical sector, leading to a revolutionary change in the pharma industry. This chapter attempts to discuss basic concept of AI in drug discovery.

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