Chapter 1
Historical Perspective of Drug Discovery and Development

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1.1 Introduction

Drug discovery and development is as old as of human civilization. They were curious from the beginning and observed keenly the nature for their survival and evolution. From their comprehension, identified the plants for their food and identified the ones which produce cure, toxic or poisonous effects to humans. Curare, a mixture of plant extracts, was applied on the arrows to immobilize the animals during the hunting in olden days in South America and later it was developed into muscle relaxant, d-tubocurarine [1]. The pharmacological basis of action of curare and the neurotransmitter acetylcholine role at neuromuscular junction was reported by Bernard and Dale, respectively [2, 3]. By trial and error method, humans tested various natural products on self and identified the useful and poisonous substances. The drug discovery evolved from natural products, synthetic, biotechnological to biopharmaceutical drugs. The concept of reductionism (drug receptor and theories [4–7]) to multiple paradigm concept transformed the drug discovery and development into a complex process [8]. This chapter will provide an overview and future scenario of history of drug discovery.

1.2 Early History and Natural Products: Drug Discovery

Ever since the existence of humans on this planet, they are exploring the nature for their daily requirements including medicines. The history of the use of medicinal herbs by Neanderthals, civilizations in Mesopotamia, Egypt and Rome is reviewed

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R. Poduri (ed.), *Drug Discovery and Development*,
https://doi.org/10.1007/978-981-15-5534-3_1

[9]. The drug discovery was influenced by the social and cultural traditions. Initially the knowledge regarding the medicinal uses of plants was transmitted through the word of the mouth from one generation to another or paintings on the caves. Majority of plant products which were depicted in the paintings are related the substances acting on brain. The identification of the medicinal use of plants was part of magic and religion [10]. It was believed that disease was due to possession demon and used to treat demon. Greeks thought that the drugs remove the imbalance in the humours which cause the disease. Greeks contributed to the rational development of the herbal drugs. Galen (130–200 AD) writings were well acclaimed (galenicals) [11]. Chinese and Arabs also contributed to the growth of the herbal drugs [12].

The connection between the west and India was mainly due to the silk road. *Atharvaveda* [13] contained the basic concepts of Indian system of medicine, *Ayurvedic* medicine. Charaka and Sushruta wrote *samhitas* dealing with drugs and surgical procedures, respectively. As per *Ayurveda*, the diet, lifestyle and environment cause the humoral imbalance, leading to the disease. The concept of personalized treatment is advocated in *Ayurveda. Ayurveda* and evidence-based medicine need to be amalgamated [14].

Several drugs have been discovered from the compounds obtained from natural products. In the early nineteenth century, several compounds were isolated from plants which were chemically modified into drugs. The first alkaline substance was isolated from the morphine in 1817 by Serturner. Acetylsalicylic acid was synthesized from salicylic acid (extracted from willow tree) to reduce the gastric irritation by Gerhardt [15]. Number of currently approved drugs are either plant products or derivatives of the natural products. A detailed account of the role played by natural products is discussed in review [12]. However, the interest in the plant products declined in the later part of the last century due to decrease in the activity of the active component on isolation or tedious extraction procedures. Recently, Harvey and co-workers reported that the use of genomic and metabolomic studies resulted in identification of antimicrobial agents from plants. The advances in the pharmacological screening methods renewed the interest in natural product [16]. The Nobel Prize in Physiology or Medicine 2015 was awarded to the discovery of two natural products: avermectin [17] and artemisinin [18] revived interest again in natural products [19]. The important contribution of natural products in drug discovery is reviewed [20].

1.3 Serendipity and Drug Discovery and Development

"The word serendipity was first coined by Horace Walpole in a letter written to his friend Sir Horace Mann in 1754. Walpole was impressed by a fairy tale he had read about the adventures of 'The Three Princes of Serendip'(an ancient name of Ceylon, now known as Sri Lanka) who were making discoveries by accidents and sagacity, of things which they were not in quest of…" [21]. Accidental discoveries played

crucial role in science. Drug discovery and development had several examples of serendipity. Louis Pasteur, an excellent experimental researcher, made several discoveries by critical observation and said, "*in the field of observation chance only favours the prepared mind"* (see Ref. [22]). The classical example of serendipity is the discovery of penicillin. Alexander Fleming observed that the fungal contaminant inhibited the bacterial growth. The saga of antibiotics started by a chance [23].

> *Traditionally, serendipity discoveries are understood as accidental findings made when the discoverer is in quest for something else. . .. . . Serendipity is more than just the irrational part of certain scientific discoveries. It cannot be denied that there are "accidental" aspects in serendipity that may sometimes be crucial* [24].

Kubinyi [22] reported the list of serendipitous discoveries in drug research. The role of the fluoride ions in the stimulation of the adenylyl cyclase leading to the formation of cAMP was surprising and could not be explained for the next two decades [25]. This started new era of ligand-receptor mediated transmembrane signal mechanisms.

Serendipitous discoveries were made in preclinical as well as clinical phases of the drug discovery. More number of discoveries by chance were made in the clinical studies. Nearly a quarter of the medicines which are prescribed are the derivatives of serendipitously discovered chemicals [26]. Serendipity played a significant role in the discovery of numerous drugs currently being used for various lifestyle diseases. Several drugs which are used for the treatment of different types of cancers are discovered by chance observation, viz., artemisinin (antimalarial), acetylsalicylic acid (rheumatism), etoposide (cathartic), leucovorin (growth factor), metformin (antidiabetic), rapamycin (antimicrobial), streptozotocin (antibiotic), thalidomide (morning sickness) and vinblastine (antidiabetic) [27].

Some of the cardiovascular drugs are due to chance observations. Discovery of dicoumarol was an accidental observation that the cattle were dying due to internal haemorrhage after feeding on sweet clover [28]. The application of the venom from the Brazilian pit viper lowered blood pressure by Sergio Ferreira and Sir John Vane lead to understand the mechanism of renin angiotensin system [29]. "*The phenotype-based small-molecule discovery approaches are beginning to complement the more established target-based approaches to cardiovascular drug discovery*" [30].

The discovery of Viagra from NO was serendipity and it was well documented in the reviews [31, 32]. Initially, the research related to NO was with respect to its role in environmental chemistry and toxicology. Later, its role in the function of immune system and as a signalling molecule was reported [32]. Zopal and co-workers showed that NO can be used to treat acute respiratory distress syndrome [33]. The major therapeutic application of NO function is sildenafil. Pfizer originally thought that sildenafil can treat hypertension. However, it later turned out to be useful to treat erectile dysfunction. The discoveries associated with NO functions in human body have many unexpected and serendipitous outcomes.

Ban [34] reviewed the serendipitous discovery of drugs, chloral hydrate, lithium, meprobamate, chlordiazepoxide, chlorpromazine, imipramine and iproniazid which

are acting on central nervous system. Serendipitous discoveries were the start of an era of psychopharmacological drug discovery and development. Later, the focus is to develop drugs having more selectivity for therapeutic targets. This resulted in less side effects and increased safety [35].

Serendipity also played role in the discovery of drugs for treating infectious diseases. The case study of levamisole indicates that choosing the right animal model can play role in successful development of drug. The metabolite of the test compound by the chickens modified to levamisole [36]. Acyclovir, used for the treatment of herpes simplex virus (HSV) infections, could be considered as serendipitous discovery [37].

Serendipity played a pivotal role in several discoveries of natural sciences. Lenox advocated for observations rather than seeing the things in laboratory training. *In every course, the student's modes of both observation and discovery should be examined, questioned, and shared with classmates* [38]. Serendipitous or chance discoveries along with the rational discoveries will contribute to provide solutions to the unmet needs of the humankind.

1.3.1 Chemistry-Stereochemistry and Allostery: Drug Discovery and Development

The discoveries in the nineteenth century in chemistry (organic chemistry) paved way for the rapid drug discovery. The concept of isomerism (Friedrich Wohler), synthesis of urea from inorganic material (Wohler) and synthesis of the mauveine, synthetic dye (William Perkin), started a new era of organic compounds as medicinal agents and in helping to understand how the drugs interact with biological systems. Louis Pasteur studied the impact of stereochemical aspects of the molecules action on the bacteria (see Ref. [39]).

The initiation of pharmacological response involves the formation of a complex between the drug/ligand and its site of action or receptor [7]. This interaction is dependent not only on the chemical structure of the drug/ligand which intern control the physicochemical properties but also spatial arrangement of the functional groups in the drug molecule. The drug-receptor interaction is highly dependent on the stereochemistry [40–43]. Further the stereochemistry of the drug will affect the pharmacokinetics and clinical pharmacology of the drug and thereby alter the concentration of the drug in the biosphere and the effect. The l-norepinephrine is 100 times more potent when compared to d-norepinephrine in producing effects at alpha-adrenoceptors due to its stereoisomerism. Easson and Stedman [44] proposed three-point interaction with the adrenoceptors. Based upon the interactions of the ligands and receptors the structure activity relationships for various classes of drugs were proposed.

Chirality is ubiquitous in the small molecules (ligands) and macromolecules of the biological systems. Majority of the drugs are racemic mixture and the

enantiomers of the chiral drugs though have same physical and chemical properties differ in pharmacological and biological activities [45]. The other enantiomer (s) pharmacodynamically may have partial agonistic-, antagonistic- or no-activity. On the other hand, it may produce a different activity or toxicity [45, 46]. In addition, the stereoisomers may have different pharmacokinetic characteristics (absorption, distribution, metabolism, and excretion (ADME) [45]. The thalidomide incidence causing the teratogenicity is good example for interconversion of the isomers in the biological systems [47, 48].

Srinivas and co-workers reviewed the issues, considerations, and regulatory requirements related to enantiomer drug development [49]. The USDFA guidance document (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-new-stereoisomeric-drugs) was issued in May 1992. As a result of the unexpected toxicity the regulatory approval process has become stringent and time consuming. Atropisomerism may give rise to geometrical isomers, diastereoisomers, or enantiomers and can interconvert may cause in design and development of new drugs and their regulations [50, 51].

The concept of allosterism was proposed as early as 1965 as the Monod–Wyman–Changeux model to explain the mechanisms involved in the action of ligands with bacterial enzymes [52]. The interest in allosterism was developed with the clinical success of the benzodiazepines [53]. Several classes of allosteric drugs affecting various biological targets were identified by both academia and pharmaceutical industry involved in allosteric drug discovery [54].

Majority of the drugs and endogenous substances act on the receptors present on the cell surface. Initial studies on characterization of drug receptor interactions are based on endogenous ligands with orthosteric site. Subsequently it is observed that the drugs can interact with other binding sites on the receptors which are known as allosteric sites. The binding to these sites can result in increased selectivity and decreased toxicity. Molecular mechanisms involved in allosteric modulation of receptor activity played a pivotal role in drug discovery and development due to innumerable number of possibilities to obtain selective drugs for various targets and to minimize the toxic effects [55, 56].

G protein coupled receptors (GPCRs) reported to interact allosterically with number of ligands. Kenakin and Laurence [56] reviewed allosteric interactions involving GPCR mechanisms and their effects. The authors discussed the functional selectivity (biased agonism and biased antagonism) and its potential therapeutic applications. The explosion of technology that has enabled observation of diverse 7TMR behaviour has also shown how drugs can have different efficacies depending upon how the ligand interacts and can elicit different effects [57].

The computational methods [58] played critical role in predicting the drug-receptor interactions [7] and effects and contributed lot to the allosterism-based drug discovery. The computational methods to identify the allosteric interactions in drug discovery and the role it can play in predicting the drug resistance and selectivity are reviewed [59–61].

Allostery in endogenous proteins produces disease and contributes to drug discovery and development. Better understanding of disease symptoms at the

molecular level and specific altered allosteric interactions can leads to innovative and safe therapies [62].

1.4 Chemical Biology and Drug Discovery and Development

The identification of correct lead via assessing its biological/pharmacological properties, and understanding of structure activity relationships are essential for successful drug development. Initially the properties of the leads were determined mainly by pharmacological methods. Pharmacological receptor characterization was done on the end organ responses. In general, in vitro and in vivo pharmacological screening methods are used to test the ligand-mediated effects. Small molecules are screened for activity using the receptor protein by either conventional or high-throughput screen methods [63]. Receptor binding assays played prominent role in the identification of the target and ligand interactions which paved ways to drug discovery [64]. Target identification, identification of transmembrane signal mechanisms and downstream pathways that mediate the effects have important roles in drug discovery [65]. Target identification, deconvolution and validation are reviewed [66].

Genetics and genetic modifications [67] greatly influenced in understanding the post drug receptor interactions and downstream pathways. CRISPR-Cas gene editing is "ready to have immediate impact in real world drug discovery" [68]. CRISPR-Cas help in identifying the target which is critical for successful drug discovery. The technology will help in to switch off /knock out the specific genes and obtain the desired mutations. Variations in the genetic composition lead to alterations in the metabolic enzymes and thereby the sojourn of the drug in the body. Hence the pharmacokinetic parameters [69] vary accordingly [70]. Genome-Wide Association Studies (GWASs) identified the human genes which are specifically associated with diseases and the targets for drug discovery [71]. Amalgamation of the network biology/ pharmacology with genetics will play prominent role in successful drug discovery and drug repurposing [72]. Genetics played a critical role in the drug development (see Ref. [73]).

Advances in biotechnology and rDNA technology produced human insulin and erythropoietin in cell culture and the monoclonal antibodies started new era of biological drugs [74]. The bioavailability of the macromolecules is very poor and require the technologies of drug delivery. Nanotechnology provides solution to site-specific delivery and increases bioavailability. The biological/toxicological properties of these engineered nanomaterials are different from the bulk materials. The safety and toxicity properties need to be tested other than conventional methods [75, 76].

Once the successful preclinical evaluation of the investigational new completed, the clinical trials (Phase I–Phase IV) and pharmacovigilance studies are carried out.

The regulatory sciences and regulations evolved and analysis and interpretation of the data are carried out by statistical methods.

1.5 Future Drug Discovery and Development

The cost of marketing a new drug is billions of US$ and it is increasing year after year due to high attrition rate in Phase III clinical trials. To overcome the failures of the drugs in various stages of clinical studies, increasing the reproducibility of the results of biomedical experiments, a better understanding of the processes in the disease states and gaining experience to manage the translational research in academic institutions are prime requirements [77].

Disruptive technologies are helpful to understand the downstream pathways involved in normal and disease state. The advent of virtual reality for the drug discovery has significant advantages for screening of the novel drugs [78]. New virtual reality methodologies are being used in the drug development. Artificial intelligence provides critical support in data mining, curation and management of the drug discovery big data [83]. AI can provide solution to drug discovery intricacies. Judicious use of these methodologies will provide better results [79]. Human induced stem cell technology is very useful for cell-based drug discovery to screen the novel molecules for lifestyle diseases [80, 81]. Organoids which are derived from stem cells resemble the original organs, and are used in drug discovery and development [82]. Multiple assays are required to determine the efficacy, selectivity, and safety of compounds during early stages of drug development to reduce attrition rates and lead to successful drug discovery [80]. Digital technologies will enhance faster and successful drug discovery to meet the unmet needs of humans.

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