Chapter

Introductory Chapter: The Modern-Day Drug Discovery

Partha Karmakar, Ashit Trivedi and Vishwanath Gaitonde

1. Drug discovery: a brief outline of 5000 years of history

The history of drug discovery and development is as old as some of the oldest human civilizations. The practice of Ayurveda in India and traditional Chinese medicines in China are over 5000-year-old therapeutic traditions that are still in practice at large. Papyrus Ebers is evidence of medicinal practice in Egypt about 3000 years ago [1–6]. The Greek and Roman medicines became popular in Europe and western Asia between ~700 BC and 200 BC [7]. The ancient Arab medicines were in practice to a great extent until 1500 AD and are still in use in the Mediterranean gulf [8, 9]. The beginning of modern era medicine can be considered from the time when Edward Jenner discovered immunization for smallpox. The development in the field was gradual until Sir Alexander Fleming discovered Penicillin in 1928; since then, the field of medicinal chemistry and drug discovery has flourished, and by the end of the twentieth century, it became a complex interdisciplinary platform primarily based on synthetic organic chemistry expanding into various biological specificities [10–13]. As a result, the global pharmaceutical market strengthened to nearly 400 billion US dollars by the year 2001 [14, 15].

2. Modern-day fabric of pharmaceutical industry

At the beginning of the twenty-first century, drug discovery research faced new challenges transforming the classical concept of drug development that was in practice for half a century. With advances in science and technology, the pharmaceutical, health care, and IT industry, accompanied by high-pace shifts in the global economy, bolstered the process of modern-day drug discovery and development to a large significance. Novel interdisciplinary research involving metal and polymer nanoparticles, liposomes, antibodies, and neo-antibiotics in both academia and industries have opened venues for precision diagnosis, targeted drug delivery, and innovative immunotherapy [16–24]. Although the classical steps in drug discovery (involving target validation, lead molecule design, chemical synthesis, pre-clinical evaluation, ADME, clinical trials and development for market of the pharmaceutical agents) are followed to date, the distribution of funding at each stage have changed due to the changing global market and healthcare policies [25]. Even though pharmaceutical companies relatively survived the recession phase of the early twenty-first century, a significant amount of budget cuts in R&D and new drug development pipeline was evident [26]. Post-recession, in the course of recovery, the collaborative efforts of the pharmaceutical and IT industry have brought state-of-the-art analytical tools that can pull multifaceted data in large quantities and predict the patients' needs and market trends [27]. This has enabled

the pharmaceutical companies to reorganize the drug discovery and development programs in a more efficient and cost-effective way. Furthermore, market research has contributed to global pharmaceutical growth that is projected to reach 1.18 trillion US dollars by 2024 [28].

The main reason of this success is the data-driven integration of every major component of pharmaceutical industries with the healthcare industries that includes hospitals, doctors, patients, and insurance companies along with the regular drug discovery units. This has transformed the classical linear drug discovery road (**Figure 1**) into a complex multidimensional map (**Figure 2**), where the whole industry is revolving around the power of the market analysis in a symbiotic fashion. Though the specific needs of different companies are different depending on their size, resources, and target market, the cumulative fabric of symbiosis is common [29]. The existing market data has accelerated the process of "new target identification." It has also helped in repurposing existing and abandoned therapeutics from different phases of drug development in an unprecedented way [30, 31]. Proper analysis of healthcare data and labor market research have shown positive impact on government policies in allotting and redistributing funds for healthcare industries and basic academic research that are closely associated to drug discovery research, which consequently helps the pharmaceutical market to grow [32, 33]. The huge success in genomics research, high-throughput screening (HTS) robotics, and gene sequencing technologies resulted a pull of publication that have reported synthesis or extraction of a cumulative of over 90 million drug-like compounds [34]. Moreover, advances in large-scale cell and tissue imaging have enabled precise location determination of the drugs and measured variety of phenotypes in cells and whole organism [35]. These advances in hardware instruments, research methodologies, and data processing synergistically contribute at various stages of drug development. The application of deep learning in leveraging these large-scale heterogeneous database is now an integral part of industrial pharmaceutical research [36]. Although machine learning (ML) is at its infant stage, it has already

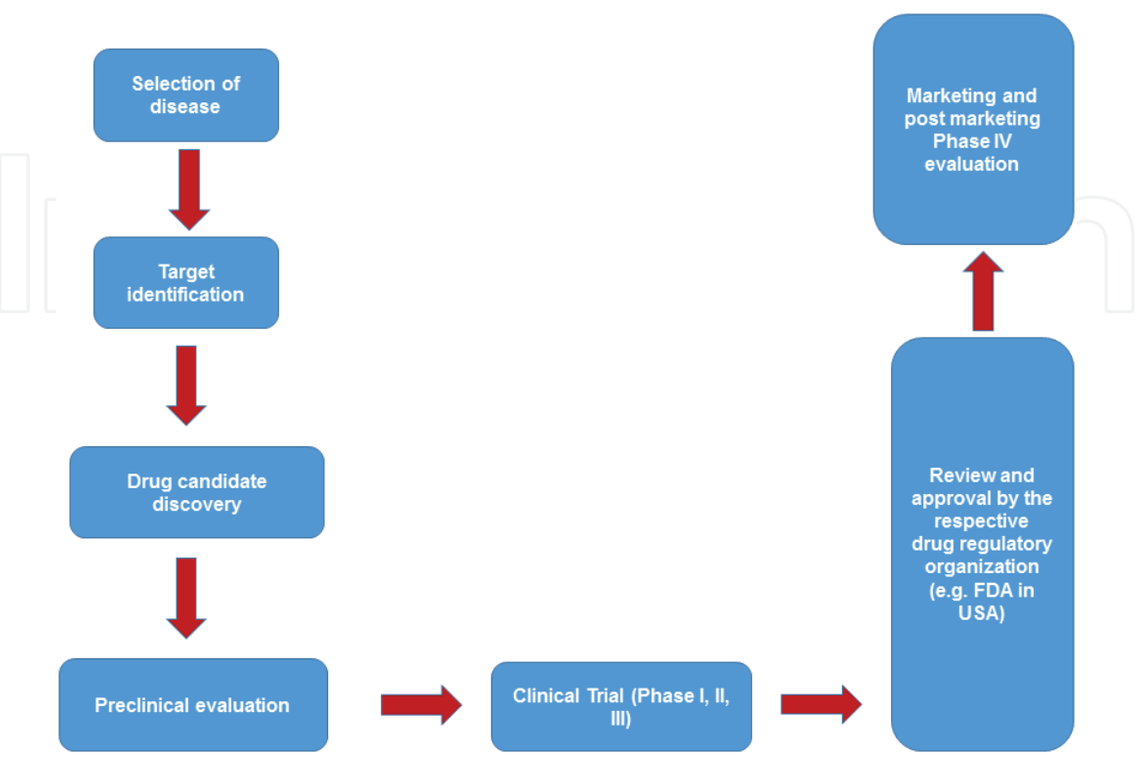

Figure 1.
Classical components of drug discovery.

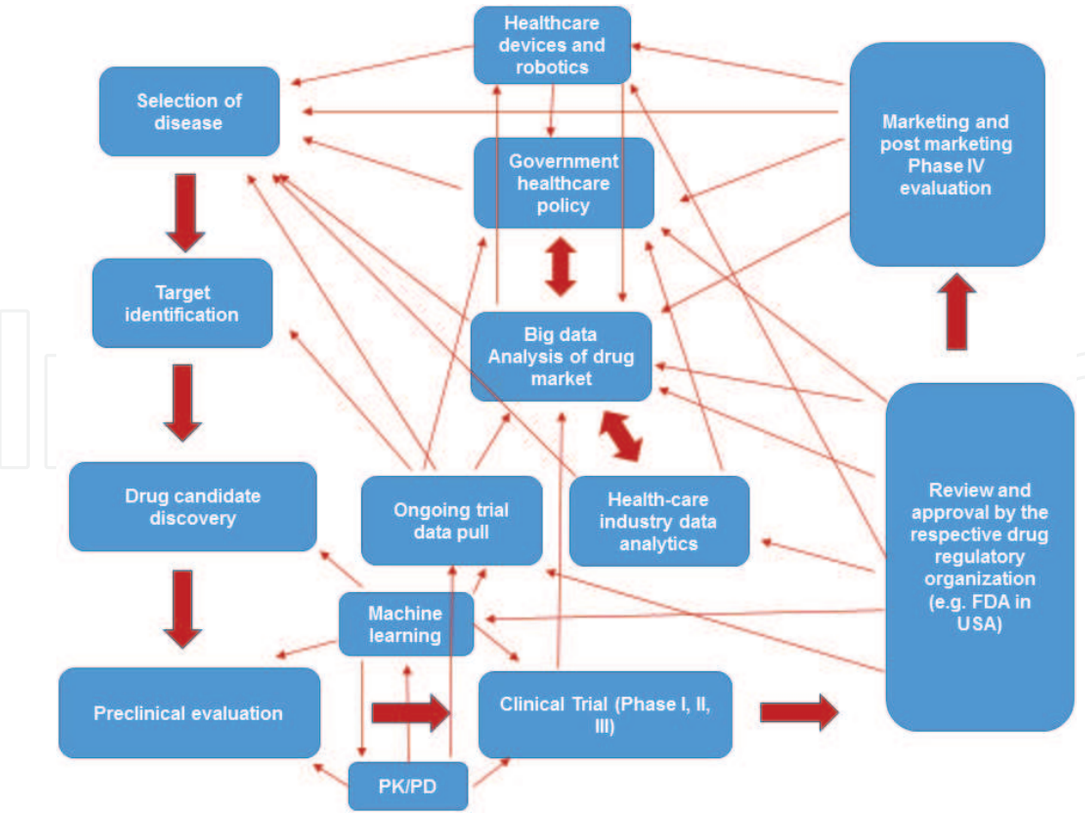

Figure 2.
Modern-day symbiotic fabric of drug discovery.

reduced the library sizes for HTS and helped to understand complex multiomic data [37, 38]. The rapid progress of different ML methods will have considerable impact on future therapies [39].

3. Importance of PK/PD in modern-day drug discovery

The historical prototype for clinical drug development was to conduct a few Phase 1 studies followed by a couple of Phase 2 studies consequently leading to multiple expensive Phase 3 trials to demonstrate the efficacy of the drug candidate. With the changing landscape and regulatory requirements, the number of clinical studies to elucidate multiple questions related to drug properties such as the mechanism of actions, pharmacokinetics (PK), pharmacodynamics (PD), and drug metabolism increased overwhelmingly prior to Phase 3 studies. The increase in the number of clinical trials has made drug development more lengthy and exorbitant. To overcome this limitation and reach patients promptly, it is imperative to utilize advanced technologies and approaches. One such approach is the PK/PD guided drug development. PK/PD modeling has been extensively employed to generate first-in-human dose predictions and selecting optimal doses for Phase 2 and Phase 3 trials. PK/PD modeling also plays an instrumental role in identifying if any dose adjustments are needed in special populations such as pediatrics and geriatrics and patients with hepatic or renal impairments [40, 41]. Additionally, PK/PD model-informed drug development (MIDD) has gained increasing momentum in recent years and is extensively used across pharmaceutical industries globally.

MIDD has become a crucial tool after receiving formal recognition in Prescription Drug User Fee Act (PDUFA) VI, thus paving a path forward to optimize drug dosing prior to approval and post-marketing and in special populations

in the absence of dedicated clinical trials. Dose optimization and clinical trial design have been most established domains of MIDD; new technologies such as artificial intelligence, ML, and real-world data (RWD), wearables along data science, have the potential to transform MIDD.

ML approaches provide a set of tools that can improve decision-making for well-specified questions with abundant, high-quality data. While using ML in the early stages of drug design, target selection, and high-throughput screening is almost standard today, the potential of ML during drug development has not been recognized. The observed data/evidence obtained during the developmental phase does not necessarily answer all the questions; thus the scope of MIDD is largely expanded with analysis of RWD to generate real-world evidence (RWE) to resolve these unanswered questions. Although RWD is obtained under less-controlled settings requiring proper interpretation of the findings, it should be considered as an attractive tool appealing for MIDD [42].

The emerging new techniques, such as portable devices, wearables, and applications (apps), may improve the dosing accuracy for patients and the quality of the collected medical information in real-world medical practice. These tools may improve the quality of electronic health records, making real-world data a reliable source for drug development and dose optimization or individualization. All these tools will make real-world data/real-world evidence a more appealing source for MIDD [43].

Along with the power of data analytics, advances in computational chemistry, and new diagnostic techniques, PK/PD modeling tools have also influenced the drug discovery research and development. These advances assist to build a comprehensive protein-receptor database, thereby enabling a defined library size for designing and optimization of a lead molecule. Along with the classical small molecule drug discovery and development, many protein and antibody-based pharmaceuticals have appeared as blockbuster drugs.

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