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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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References

- [1] Sharma T, Rawal G. Role of ayurveda in tumorigenesis: A brief review. *International Journal of Green Pharmacy (IJGP)*. 2012;**6**(2):93-101
- [2] Mamtani R, Mamtani R. Ayurveda and yoga in cardiovascular diseases. *Cardiology in Review*. 2005;**13**(3):155-162
- [3] Khan S, Balick MJ. Therapeutic plants of Ayurveda: A review of selected clinical and other studies for 166 species. *The Journal of Alternative & Complementary Medicine*. 2001;**7**(5):405-515
- [4] Glazier A. A landmark in the history of Ayurveda. *The Lancet*. 2000;**356**(9235):1119
- [5] Farquhar J. *Knowing Practice: The Clinical Encounter of Chinese Medicine*. London: Routledge; 2018
- [6] Law BYK, Wu AG, Wang MJ, Zhu YZ. Chinese medicine: A hope for neurodegenerative diseases? *Journal of Alzheimer's Disease*. 2017;**60**(s1):S151-S160
- [7] Ackerknecht EH, Haushofer L. *A Short History of Medicine*. Baltimore: Johns Hopkins University Press; 2016
- [8] Saad B, Azaizah H, Said O. Tradition and perspectives of Arab herbal medicine: A review. *Evidence-based Complementary and Alternative Medicine*. 2005;**2**(4):475-479
- [9] Bynum W, Porter R. Arab-Islamic medicine. In: *Companion Encyclopedia of the History of Medicine*. London: Routledge; 2013. pp. 702-753
- [10] Cates J, Christie R. Subacute bacterial endocarditis. A review of 442 patients treated in 14 Centres appointed by the penicillin trials Committee of the Medical Research Council. *Quarterly Journal of Medicine*. 1951;**20**(78):93-130
- [11] Duggleby HJ, Tolley SP, Hill CP, Dodson EJ, Dodson G, Moody PC. Penicillin acylase has a single-amino-acid catalytic centre. *Nature*. 1995;**373**(6511):264
- [12] Heath JR, Ribas A, Mischel PS. Single-cell analysis tools for drug discovery and development. *Nature Reviews Drug Discovery*. 2016;**15**(3):204
- [13] Kelm JM, Lal-Nag M, Sittampalam GS, Ferrer M. Translational in vitro research: Integrating 3D drug discovery and development processes into the drug development pipeline. *Drug Discovery Today*. 2019;**24**(1):26-30
- [14] Walker N. Impacts of Glocalization on the Pharmaceutical Industry. 2019. Available from: <https://www.pharmasalmanac.com/articles/impacts-of-glocalization-on-the-pharmaceutical-industry>
- [15] Pharmaceutical market: Worldwide revenue 2001-2018. 2019. Available from: <https://www.statista.com/statistics/263102/pharmaceutical-market-worldwide-revenue-since-2001>
- [16] Yaari Z, Da Silva D, Zinger A, Goldman E, Kajal A, Tshuva R, et al. Theranostic barcoded nanoparticles for personalized cancer medicine. *Nature Communications*. 2016;**7**:13325
- [17] Lee H, Lee Y, Song C, Cho HR, Ghaffari R, Choi TK, et al. An endoscope with integrated transparent bioelectronics and theranostic nanoparticles for colon cancer treatment. *Nature Communications*. 2015;**6**:10059
- [18] Karmakar P, Lee K, Sarkar S, Wall KA, Sucheck SJ. Synthesis of a liposomal MUC1 glycopeptide-based immunotherapeutic and evaluation of the effect of L-rhamnose targeting on cellular immune responses. *Bioconjugate Chemistry*. 2015;**27**(1):110-120

- [19] Karmakar P, Gaitonde V. Promising recent strategies with potential clinical translational value to combat antibacterial resistant surge. *Medicine*. 2019;**6**(1):21
- [20] Catalano JG, Gaitonde V, Beesu M, Leivers AL, Shotwell JB. Phenoxide leaving group SNAr strategy for the facile preparation of 7-amino-3-aryl pyrazolo [1, 5-a] pyrimidines from a 3-bromo-7-phenoxy pyrazolo [1, 5-a] pyrimidine intermediate. *Tetrahedron Letters*. 2015;**56**(44):6077-6079
- [21] Nishimura Y, Gautam R, Chun T-W, Sadjadpour R, Foulds KE, Shingai M, et al. Early antibody therapy can induce long-lasting immunity to SHIV. *Nature*. 2017;**543**(7646):559
- [22] Gaitonde V, Sucheck SJ. Antitubercular drugs based on carbohydrate derivatives. *Carbohydrate Chemistry: State of the Art and Challenges for Drug Development: An Overview on Structure, Biological Roles, Synthetic Methods and Application as Therapeutics*. 2015:441-478
- [23] Thanna S, Lindenberger JJ, Gaitonde VV, Ronning DR, Sucheck SJ. Synthesis of 2-deoxy-2, 2-difluoro- α -maltosyl fluoride and its X-ray structure in complex with *Streptomyces coelicolor* GlgEI-V279S. *Organic & Biomolecular Chemistry*. 2015;**13**(27):7542-7550
- [24] Hossain MK, Vartak A, Karmakar P, Sucheck SJ, Wall KA. Augmenting vaccine immunogenicity through the use of natural human anti-rhamnose antibodies. *ACS Chemical Biology*. 2018;**13**(8):2130-2142
- [25] Gilliland CT, Zuk D, Kocis P, Johnson M, Hay S, Hajduch M, et al. Putting translational science on to a global stage. *Nature Reviews Drug Discovery*. 2016;**15**(4):217
- [26] Clark JW. Financial Narratives of US Biotechnology Companies Before, During, and After the Great Recession. 2015. Available from: https://fisherpub.sjfc.edu/cgi/viewcontent.cgi?article=1218&context=education_etd; https://fisherpub.sjfc.edu/education_etd/217
- [27] Joshi RR, Sonavane U, Jani V, Saxena A, Koulgi S, Uppuladinne M, et al. Turbo Analytics: Applications of Big Data and HPC in Drug Discovery. In *Structural Bioinformatics: Applications in Preclinical Drug Discovery Process*. Switzerland: Springer; 2019. pp. 347-374
- [28] EvaluatePharma World Preview 2019, Outlook to 2024. 2019. Available from: <https://www.evaluate.com/thought-leadership/pharma/evaluatepharma-world-preview-2019-outlook-2024>
- [29] Wagner JA, Dahlem AM, Hudson LD, Terry SF, Altman RB, Gilliland CT, et al. Application of a dynamic map for learning, communicating, navigating, and improving therapeutic development. *Clinical and Translational Science*. 2018;**11**(2):166-174
- [30] Karaman B, Sippl W. Computational drug repurposing: Current trends. *Current Medicinal Chemistry*. 2019;**26**(28):5389-5409
- [31] Nordon G, Koren G, Shalev V, Horvitz E, Radinsky K. Proceedings of the AAAI Conference on Artificial Intelligence. Separating Wheat from Chaff: Joining Biomedical Knowledge and Patient Data for Repurposing Medications. Vol. 33, No 01: AAAI-19, IAAI-19, EAAI-20; 2019. IAAI Technical Track: Emerging Papers. Available from: <https://www.aaai.org/ojs/index.php/AAAI/article/view/5017>
- [32] Cinaroglu S. Politics and health outcomes: A path analytic approach. *The International Journal of Health Planning and Management*. 2019;**34**(1):e824-e843

- [33] Zolbanin HM, Delen D, Sharma SK. The strategic value of big data analytics in health care policy-making. *International Journal of E-Business Research (IJEBR)*. 2018;**14**(3):20-33
- [34] Kim S. Getting the most out of PubChem for virtual screening. *Expert Opinion on Drug Discovery*. 2016;**11**(9):843-855
- [35] Boutros M, Heigwer F, Laufer C. Microscopy-based high-content screening. *Cell*. 2015;**163**(6):1314-1325
- [36] David L, Arús-Pous J, Karlsson J, Engkvist O, Bjerrum EJ, Kogej T, et al. Applications of deep-learning in exploiting large-scale and heterogeneous compound data in industrial pharmaceutical research. *Frontiers in Pharmacology*. 2019;**10**:1-16
- [37] McGaughey GB, Sheridan RP, Bayly CI, Culberson JC, Kretsoulas C, Lindsley S, et al. Comparison of topological, shape, and docking methods in virtual screening. *Journal of Chemical Information and Modeling*. 2007;**47**(4):1504-1519
- [38] Johnson KW, Shameer K, Glicksberg BS, Readhead B, Sengupta PP, Björkegren JL, et al. Enabling precision cardiology through multiscale biology and systems medicine. *JACC: Basic to Translational Science*. 2017;**2**(3):311-327
- [39] Ekins S, Puhl AC, Zorn KM, Lane TR, Russo DP, Klein JJ, et al. Exploiting machine learning for end-to-end drug discovery and development. *Nature Materials*. 2019;**18**(5):435
- [40] Bonate PL, Howard DR. *Pharmacokinetics in Drug Development: Problems and Challenges in Oncology*. Vol. 4. Switzerland: Springer; 2016
- [41] Katherine Dunnington NB, Brandquist C, Cardillo-Marricco N, Di Spirito M, Grenier J. *Application of Pharmacokinetics in Early Drug Development*. Rijeka: IntechOpen; 2018
- [42] Marshall S, Madabushi R, Manolis E, Krudys K, Staab A, Dykstra K, et al. Model-informed drug discovery and development: Current industry good practice and regulatory expectations and future perspectives. *CPT: Pharmacometrics & Systems Pharmacology*. 2019;**8**(2):87-96
- [43] Wang Y, Zhu H, Madabushi R, Liu Q, Huang SM, Zineh I. Model-informed drug development: Current US regulatory practice and future considerations. *Clinical Pharmacology & Therapeutics*. 2019;**105**(4):899-911