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Review Article

Advances in Drug Discovery: Navigating Challenges and Embracing Innovation

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Abstract:

It takes ten to fifteen years for a compound to progress from its identification to regulatory approval as a drug. Drug discovery is complex and resource-intensive process in which more than 90% of compounds never make it from bench to bedside and eventually get rejected during the development process. Experimental drugs failures often occur due to poor target selection, inadequate preclinical models, unforeseen toxicity, lack of efficacy in human trials, and the complexity of disease mechanisms, which make it difficult to predict drug responses accurately. Additionally, drug discovery is slowed down by a lack of collaboration between academia and industry, limiting the timely exchange of knowledge and expertise. Artificial intelligence (AI) is becoming an important tool in drug discovery, offering new possibilities to overcome existing challenges. It can help researchers identify better drug targets, make the screening process more efficient, and optimize drug design, which could speed up development and improve success rates. However, use of AI is associated with certain drawbacks such as potential exacerbation of healthcare gaps, protection of sensitive patient data and a need for informed consent. This review aims to discuss key challenges that hinder drug development process and explore future directions to enhance the efficiency of drug discovery.

Keywords: Artificial intelligence; Disease mechanism; Drug discovery; Drug failure; Personalized medicine.

Introduction

The journey of a new drug from target identification to market approval takes ten to fifteen years, and depending on the therapeutic area, it might cost in the range of $314 million to $4.46 billion [1]. The developmental cost rises as the investigational agent progresses into the different stages, and it may fail to progress into the next stage for various reasons such as lack of clinical efficacy, toxicity or lack of funding. Despite the technological advances and rapid accumulation of knowledge, drug discovery is still somewhat stalling.

Even with significant time and financial resources invested, the overall success rate of developing a new drug from initial concept to regulatory approval is only 7.9% [2]. For instance, in the case of tuberculosis only two new drugs were approved by the Food and Drug Administration (FDA) over the last 50 years [3]. First-in-class drugs target novel biological pathways that have not been previously explored in clinical settings. There is high uncertainty about whether these targets will yield the desired therapeutic effect and high probability of observing off-target interactions. In contrast, modifying existing drugs involves well-characterized mechanisms, reducing the risk of unexpected failures [4]. A review of European drug approvals from 2000 to 2014 found that out of 1,345 newly approved medications, 51% were slightly modified versions of already existing chemical entities that did not offer improved therapeutic effect, and only 1% were considered innovations in therapeutic management [5]. Despite challenges, there was encouraging progress in some categories - between 2015 and 2021 FDA approvals of biological drugs increased with monoclonal antibodies (mAbs) being the most widely approved category [6].

Although a drug candidate may perform well and produce favorable outcomes during preclinical investigations, this success does not always translate into clinical efficacy or safety in humans. Oftentimes results of clinical studies may reveal new various limitations such as unforeseen side effects, reduction in efficacy and potential drug-drug interactions that were not apparent at the preclinical stage due to complexity of disease mechanisms in humans and below average predictive potential of studied animal models. Lack of collaboration between academia and industry may also be one of the factors contributing to delay in progress and scarcity of successful approvals as important information regarding new findings and regulatory measures does not reach in a timely manner or may get completely lost.

This review aims to explore the key obstacles in drug discovery, from scientific and technological limitations to financial and regulatory barriers, as well as new developments such as the emergent use of artificial intelligence (AI). By analyzing these challenges, we can gain insights into potential solutions that could reshape the future of pharmaceutical research and development.

Methodology

The literature used in this review was selected from peer-reviewed articles published between 2015 and 2020 from databases such as PubMed, Scopus and Google Scholar using search terms such as ‘drug discovery’, ‘pharmacological innovations’, ‘AI in drug development’, ‘challenges of drug discovery’. Papers were selected based on relevance to the theme, content quality and recency. No protocol of systematic review was used. Generative AI tools were not used in the preparation of this manuscript. Minor language editing tools were used to improve clarity and grammar.

Traditional drug discovery and it’s challenges

High Failure Rates

For pharmaceutical companies and academic institutions, progressing a drug candidate to Phase I clinical trials after extensive preclinical optimization is a significant accomplishment. However, the reality is that nine out of ten drug candidates that passed preclinical stages fail at some point during Phase I, II, or III of clinical trials and do not receive regulatory approval [7]. The percentage of failure during drug discovery is even higher than 90% if we consider the fact that many compounds do not make it past the preclinical stage. The large divide between preclinical and clinical research is oftentimes referred to as “the valley of death” [8].

While there are a number of reasons for drug failure during clinical trials, the primary reason at this stage appears to be due to inadequate efficacy. For example, a study of 640 phase III clinical trials by Huang et al. reported that out of the 344 (54%) failed trials 195 (57%) were due to lack of demonstrated efficacy, 59 (17%) failed due to safety concerns and 74

(22%) failed because of commercial reasons. Compounds developed by small and medium-sized companies were most likely to fail due to commercial reasons [9]. Interestingly, potentially effective drugs may also fail in demonstrating efficacy, due to several factors such as flaws in the design of the study, an unsuitable statistical endpoint, or performing an underpowered clinical trial where the number of patients is too small to be able to reject the null hypothesis [10]. In January 2025 navacaprant, a potential agent for treatment of major depressive disorder (MDD) failed to demonstrate statistically significant improvement on the primary endpoint compared to placebo [11].

Demonstrated efficacy also does not necessarily guarantee drug approval. For instance, Atabecestat is a β-secretase1 (BASE1) inhibitor that was intended to treat Alzheimer's disease that initially showed promising results such as a stable reduction in β-amyloid peptide (Aβ) levels, however it was discontinued due to reports of liver toxicity among patients [12]. Table 1 below shows more examples of drug candidates that failed during different stages of drug development in recent years [13-17]. The data was acquired from open access articles published between 2019 and 2025.

Table 1: Drug Candidate Failures at various development stages.

Drug name	Drug class	Year of failure	Drug discovery and development stage	Reason for failure
CNP520 (Umibecestat)	Inhibitor of the beta-site amyloid precursor protein cleaving enzyme-1	2019	Phase II-III clinical studies	Worsened cognitive decline in Alzheimer's patients [13]
Ziritaxestat	Small-molecule, selective autotaxin inhibitor	2021	Phase III clinical studies	Did not improve clinical outcomes compared with placebo in patients with idiopathic pulmonary fibrosis [14]
Lotiglipron	Small-molecule glucagon-like peptide-1 receptor agonist	2023	Phase II clinical trial	Indicated elevated liver enzymes, suggesting potential liver toxicity [15]
BIIB105	Antisense oligonucleotide for amyotrophic lateral sclerosis (ALS)	2024	Phase I-II clinical trial	Treatment did not result in a reduction in levels of plasma neurofilament light chain and had no impact on measures of function, breathing and strength [16]
Sozinibercept	*VEGF-C and VEGF-D inhibitor for* wet age-related macular degeneration	2025	Phase III clinical trials	*No difference observed in primary and secondary endpoints compared to standard of care [17]*

Complexity of disease mechanisms

Understanding the molecular mechanism of the target disease, its etiology and the compounds' mechanism of action are crucial for drug discovery. This will reduce the probability of failure in the more advanced stages of drug development and help in avoiding general toxicity, inappropriate drug target or interference of the host [3].

To understand the molecular mechanism of the disease, we must begin by examining the starting point and the condition's potential cause. The studies of disease etiology are complicated by the fact that a disease can be caused by a wide variety of factors such as genetic (higher susceptibility, inheritance, SNPs), epigenetic (methylation, miRNA), environmental (exposure to toxic substances, habits) and others such as age, pre-existing conditions, or nutrition [18]. These factors often act in combination and are closely linked

to how the disease progresses. However, studies of disease etiology and progression are complicated by the fact that the majority focus on researching the activity of a single or a limited number of biological molecules, but almost all disease processes involve a complex cascade of interactions between hundreds of chemical entities within the organism [19]. Genetic architecture of Alzheimer's disease involves 81 loci in the genome each of which individually may contribute to overall susceptibility to this disease [20].

The only preclinical systems that allow to observe progression of disease and the effect of the studied compound in a complex living organism are animal models. While some are more similar in normal and disease physiology to humans than others, such as pigs, their predictive capability is still far from ideal [21]. Animals models used most often in preclinical studies are represented by rodents and non-human primates [22]. Some of the factors contributing to complexity of disease mechanism are summarized on Figure 1.

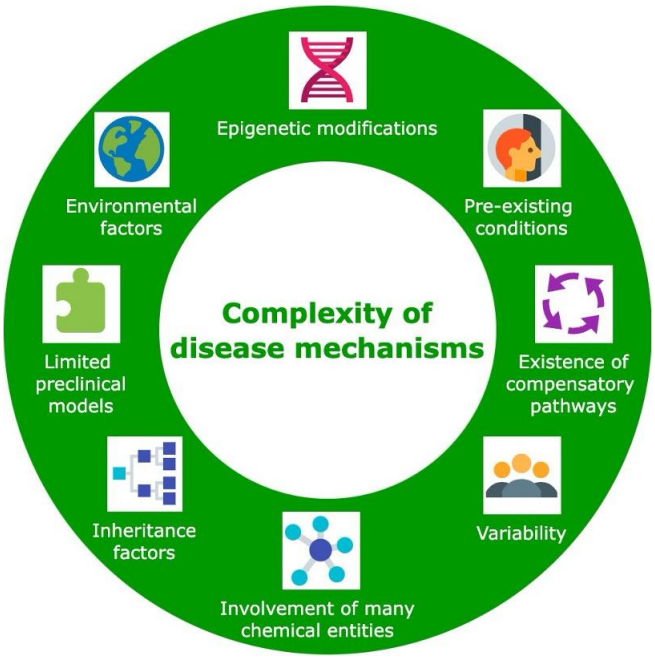

Figure 1: Complexity of disease mechanisms.

Interestingly, the FDA does not require elucidation of mechanism of action for a drug to be approved, and around 10-20% of the currently approved drugs do not have a known molecular target or certain mechanism of action [23]. For example, lithium used as first-line treatment of bipolar disorder does not have a clear mechanism that would explain its role in mood stabilization of patients despite having several unrelated theories and being effectively used for more than two centuries [24]. Even though some drugs may show clinical efficacy and be used despite a lack of knowledge about the way in which they exert their effect, understanding how they affect the drug target and off-target molecules could aid in the development of new generations of compounds with higher efficacy, lesser side effects and production costs.

Target Validation

The concept of target validation varies depending on the context but generally refers to the technical assessment of whether a target plays a crucial role in disease process and whether its pharmacological modulation could be effective in a specific patient population [25]. However, the process of target validation is complicated due to the fact that oftentimes there are fundamental differences between the course of disease in studied animal models and real humans [7]. A literature search of articles published from 2014 to 2024 revealed that the number of articles predicting potential drug-target interactions was increased, as well as the overall use of computational target identification and validation methods [26], however many of these computational predictions lack data regarding experimental validation.

Interestingly, there are a number of techniques available to assess the suitability of developmental agents targeting transcription factors and their protein interactions, something that was previously thought to be impossible. For instance, Nutlins (Nutley inhibitors), a class of compounds belong to cis-imidazoline analogs, found to serve as inhibitors of p53-MDM2 binding, which is p53 a known tumor suppressing protein largely controlled by MDM2. To validate whether nutlins actually inhibit the p53-MDM2 interaction and if so how, the crystal structure of MDM-Nutlin-2 complex was analyzed and inhibition was assessed using surface plasmon resonance technology [27].

One of the pitfalls of target validation observed, particularly in studies of new cancer treatments is the misinterpretation of correlative clinical data as causative, as two variables may be affected by an outside confounding factor and the association observed is due to chance [28]. For instance, an increase in expression of hypoxia-inducible factor (HIF) is associated with tumor growth, adaptation and poor prognosis for the patients [29]. However, this does not necessarily mean that HIF aids in tumor growth and increased malignancy, it could also indicate that as tumors increase in size their blood supply becomes insufficient and the increased expression of HIF is a response to these hypoxic conditions, or the observed association may be simply correlative [28]. Therefore, studying the nature of the relationship between a potential drug target and the observed effect is one of

the concerns that need to be addressed during the target validation process.

Toxicity and side effects

Failure of the drug due to safety concerns is the third reason for abandoning potentially viable compounds [9]. While finding and validating a drug target is an important step in drug discovery, researchers must think beyond the target-specific effects of the drug because safety issues and side effects usually arise due to off-target interactions [30]. Some compounds, despite their demonstrated efficacy, are not practical or safe to use in real life conditions because of their toxicity profiles and potential side effects. The failure of clinical drug development due to lack of efficacy does not necessarily mean the drug candidates are ineffective. More often, they fail to demonstrate sufficient efficacy in the disease-targeted organs at the maximum tolerable dose (MTD), which already causes toxicity in healthy organs [7]. While these drugs would work at higher doses, patients cannot tolerate the associated toxicity.

For instance, overexpression of endoplasmic reticulum oxidoreductin-1α (Ero1α) protein that is necessary for oxidative protein folding in the endoplasmic reticulum (ER) is associated with poor prognosis in many types of cancer such as lung cancer [31], gastric cancer [32], colorectal cancer [33] and pancreatic cancer [34]. EN460 is a small molecular inhibitor of Ero1α that works to prevent re-oxidation of Ero1α by competing with its FAD cofactor [35]. While EN460 demonstrates strong specificity for Ero1α, the drug's potency in vivo is quite low and resulted in various toxic effects due to nonspecific interactions with free thiols [35], making it an unsuitable target for clinical usage in real patients, despite being an effective inhibitor [36].

Determining off-target interactions of new drug entities may lead to accumulation of new data regarding the molecular mechanisms of the drug's side effects. For example, panobinostat is a histone deacetylase (HDAC) inhibitor that prevents binding of histones to certain regions of DNA and used for the treatment of multiple myeloma. However, hypothyroidism is one of the major reported side effects observed following drug administration. A method called thermal proteome profiling (TPP) was used for detection of four off-target proteins one of which was found to be phenylalanine hydroxylase (PAH) [37]. Interestingly, in vivo studies showed that panobinostat was bound to rat liver PAH during enzymatic assays, which resulted in the inhibition of PAH and a consequently decreased in tyrosine levels leading to a discovery possibly explaining the observed side effect of hypothyroidism [38]. Therefore, the use of TPP and enzymatic assays early on in the drug development process could help researchers gain a better understanding of the investigational drug's side effect before transitioning into animal toxicology studies [39].

Personalized Medicine and Variability

Although the same diagnosis may manifest with some differences among patients, treatments are usually administered according to a standard protocol that rarely considers such variability. Thus, personalized medicine, also referred to a precision medicine, aims to collect and analyze patients' data from genomics and proteomics for provision of more individualized treatment options and to be able to precisely predict drug responses [39]. Personalized medicine has the potential to revolutionize medical spheres, such as diagnosis and preventive care as well as to customized treatment and clinical research to each individual patient [40]. However, it has several challenges; for example, targeting of certain proteins as a personalized drug target, proved to be challenging to implement at a large scale for several reasons. First, the diverse and heterogenous nature of proteins allows them to exist in different proteoforms, meaning that the protein product of a single gene may result in many structural forms due to genetic variation, alternative splicing and post-translational modifications [41]. As structure and form of the protein are closely related to its function, there is a necessity to precisely identify the particular proteoforms that could be used as a suitable drug target for a particular disease model. Secondly, complications of drug delivery to the desired site may arise because of localization of proteins to certain cellular structures as well as differences of protein expression in tissues [39].

One of the recently developed concepts that could shape the future of precision medicine is digital twin – a digital model that offers a holistic view of individual's biological systems by integrating data from genomics, proteomics, data from wearable devices and reported from patients themselves [42]. However the use of digital twins is associated with challenges similar to those faced by artificial intelligence such as quality of data collection and interpretation, privacy and security concerns, and ethical considerations [43]. Li et al. (2025) suggest that personalized treatment may be developed by organizing factors pertaining to disease in a network and analyzing it in terms of changes observed in corresponding proteins [44]. Digital twin could be used for modeling organ or tissue-specific progression of the disease as well as how a patient will respond to therapy over time [45].

However, since a digital twin is a relatively new development, it does not yet have clearly articulated and comprehensive methodology.

In addition, development of patient-specific disease models requires the availability of large data banks on genomics and proteomics, as well as equal representation of genders and different ethnicities in clinical trials [21]. Because personalized medicine heavily depends on availability of sensitive patient data for analysis, it is important to ensure that such data is securely guarded to prevent any leaks and maintain trust and compliance [40]. Another challenge facing personalized medicine, is treatment cost, which needs to be considered when developing drugs for personalized medicine, as patients may be unable to afford treatment despite its efficacy. Nivolumab, an example of targeted therapy involving monoclonal antibodies (mAbs) in lung cancer treatment has shown efficacy exceeding 70%, however it is financially challenging to obtain for patients and healthcare systems due to its high cost [46].

Lack of Collaboration Between Disciplines

Due to the more publication-oriented nature of research in academia only a very small number of investigators actually get to partner and work collaboratively with industry representatives to proceed from bench research to clinical studies [47]. This leads to a formation of a large gap between the drug 'discovery' and 'development' stages.

For example, proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that regulates the metabolism of cholesterol, and its activity is associated with higher levels of low-density lipoprotein (LDL) in blood plasma [48]. Analysis of papers published over the last twenty years on the discovery of PCSK9 and development of its inhibitors showed that 9286 scientists and 4203 institutions collaborated and contributed to the body of knowledge regarding this enzyme [49]. However, 40% of collaborations were within the same institution and out of the 60% that involved inter-institutional collaborations only 20% were with pharmaceutical companies [49].

Although new treatments may originate from academia or government research, they cannot be widely distributed without industry involvement. Notably, among around a hundred agencies that participated in the development of COVID-19 vaccine 85% were represented by the private industry [50]. Collaboration between industry and academia is necessary because academic researchers may face monetary restrictions that prevent them from advancing to further stages of drug development as well as lack expertise necessary to make the compound appealing to the industry [47]. Today more than ever collaboration in science is made easier by the existence of online communication. Qualified specialists all across the globe are able to work together to gather and analyze experimental data with relative ease.

Financial Constraints and Regulatory Challenges

Translational research aims to bridge the gap between basic scientific research and clinical practice [8]. Unlike basic research, translational research is more difficult and costly, because it requires testing in complex organisms like animals and humans. When a drug candidate successfully moves through the preclinical stages of development the risks associated with its failure decrease, however the cost of experiments rises exponentially. In academia, progress tends to be considerably slower compared to industry partly because of financial constraints. A substantial part of research financing from a grant is dedicated to purchasing consumable reagents and equipment as well as salaries for employees, leaving little for further continuation to clinical trials [47]. Due to differences in funding, structure, and priorities, projects that take years in academia can take months to complete in industry [51]. Small and medium-sized companies are more likely to discontinue studies of potentially viable compounds due to a lack of funding [9]. In the light of recent findings academic industry partnership (AIP) is becoming more of a necessity than an optional addition, if the goal is to speed up and enhance drug discovery efforts. Notably, gap funding programs such as translational research grants, proof of concept programs, startup accelerators and philanthropic venture funds help to recruit and secure more outside capital for development of new drug products [52]. An example of proof-of-concept gap funding program is The Translational Therapeutics Accelerator (TRxA), established in 2022 by the Critical Path Institute (C-Path), which designed to help bridge the "valley of death" in drug development. This global initiative provides academic researchers with the financial resources and strategic guidance necessary to advance new therapies from early-stage of discovery to patient care [52]. It also supports third-party validation of key research findings by recruiting outside organizations to reproduce the observed results.

Regulatory challenges in drug discovery arise due to strict requirements imposed by health authorities to ensure the safety, efficacy, and quality of new drugs. These challenges can delay the development, increase costs, and limit innovation. The length of a standard drug development procedure

being 12 to 15 years is in part due to the need to adhere to regulatory guidelines and the time necessary to review and correct the research documentation. Historically, it was shown that during emergency situations the length of drug development timeline can be shortened dramatically with the support of regulatory organizations. For example, the development of COVID-19 vaccines was sped up due to the declaration of an emergent infectious disease (EID); and the use of conditional marketing authorization (CMA) [53]. With the usual regulatory obstacles removed, the vaccine was developed in about eight months, whereas the median development time from clinical research initiation to obtaining marketing authorization is more than seven years for drugs approved by European Medicines Agency (EMA) between 2021 and 2022 [53].

Usually, academic researchers have lower understanding of the regulatory affairs and how to navigate them than their industry counterparts, which is one of the reasons why collaboration would have mutual benefits [52]. O'Dwyer et al. (2023) identified four main phases that university–industry collaborations go through: the embryonic phase, initiation, engagement, and the established phase [54]. In the embryonic phase academic researchers identify potential areas of interest that could lead to industry collaboration, during the initiation phase that happens after 2 – 3 years network members get to establish trust, share goals and communicate their strategies and needs. Third engagement phase (years 3-7) is characterized by sharing knowledge, experience and funds, whereas in the fourth established phase after year 8 is marked by first central results and growth in size [54]. Based on that study, it is evident that university-industry collaborations need time, resources and mutual understanding of common and individual goals. Figure 2 shows an example of collaboration network that involves several academic institutions, pharmaceutical companies and government organizations. Achievement of success in drug discovery heavily depends on the establishment of collaboration networks in which knowledge and resources are shared to reach a common goal.

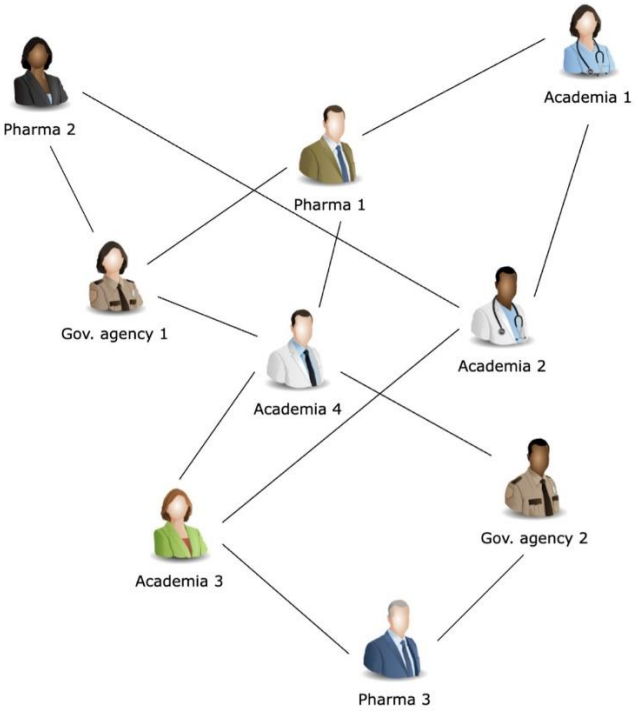

Figure 2: Collaboration between academia, government and industry.

Regulatory challenges in drug discovery require a balance between ensuring patient safety and promoting innovation. Special incentives exist to promote efforts of drug discovery by pharmaceutical companies, and they can largely be divided into push and pull incentives. Push incentives help sponsors by lowering research and development expenses, whereas pull incentives help by increasing profits from the market [55]. However, these incentives, it appears, have not led to sufficient investment for breakthrough drugs or solutions to unmet health needs, partly due to the fact that they primarily focus on the financial interest of pharmaceutical companies, which are not the only contributors to innovative health products [56].

Interventional Measures of the Challenges

Enhance Collaboration Efforts – Academia, Industry and Beyond

Pharmaceutical businesses aim to create practical and efficient solutions, conserve their value and maximize profits, whereas academic institutions are more likely to pursue high-risk and innovative endeavors [50], but this may actually be an advantage as illustrated by some cases of productive and mutually beneficial AIP. Prominent collaborations between the pharmaceutical industry and academia include partnerships such as AstraZeneca with Columbia University, Pfizer with the University of California at San Francisco, Monsanto with the University of Washington, and GlaxoSmithKline (GSK) with Harvard University, among others [57].

Similarly, the Wyss Institute for Biologically Inspired Engineering at Harvard University allowed for collaboration of faculty with industry professionals using the 'technology innovation funnel' model that gives academia an opportunity to develop creative ideas while refining and commercializing them with representatives from industry for a future real-life application [50].

Success of a partnership between academic institutions and pharmaceutical companies requires consideration of factors, such as acceptance of cultural differences and clear communication, despite potential differences in priorities regarding research, innovation and education [58]. Consistent communication and collaboration among research institutions, industry and sponsors is especially important during phase III clinical trials, due to a necessity to conduct large-scale studies that oftentimes span over multiple regions or continents and involve hundreds and thousands of participants [2].

Collaboration of large pharmaceutical corporations with artificial intelligence-driven drug discovery (AIDD) companies could also be beneficial in way that it allows for an exchange of computational models, proprietary datasets and finances [59].

Funding and Incentives

Clinical studies by academic researchers are much less supported by government organizations compared to basic science research, this is because translational efforts can be perceived as less favorable by some funding agencies . In a recent survey of academic researchers, with experiences in both academic clinical trials and industry-sponsored trials; found that academic trials have significantly less financial support at the time of their conduction compared to industry-sponsored trails [60]. Since grants provided by government organizations for academic research purposes are mostly insufficient to conduct clinical trials, academics have two ways in which they can conduct clinical trials: 1) by collaborating with industry partners, which can fulfill the monetary and regulatory knowledge gaps; 2) by participating in government-funded programs that support drug discovery efforts by academics.

However, existing push and pull incentives have failed to lead to sufficient investment for breakthrough drugs or solutions to unmet health needs. For instance, in the case of antibiotic development limitations such as restricted use and growing antibiotic resistance over time lead to insufficient market reward and despite their need and importance for the society as a whole antibiotic development is still stalling [61]. Additionally, despite the existence of incentives such as the Orphan Drug Act to encourage development of treatments for rare diseases challenges that discourage this pursuit such as limited knowledge of disease mechanism, low participation in clinical trials and flawed trial design still remain [62]. Since large companies are not the only contributors to biomedical progress, the current form of incentives needs to be revisited and modified to allow exchange of knowledge and involvement of more contributors, such as non-pharmaceutical firms to provide technological support and academic researchers to counter declining efficiency [56].

Innovations in Drug Discovery: Emergent Use of Artificial Intelligence

The introduction of artificial intelligence (AI) is revolutionizing many scientific spheres such as mathematics, chemistry, physics and medicine by making it easier to analyze large amounts of data in a relatively short timeframe. Traditional methodologies of drug discovery primarily rely on resource-intensive and prolonged experiments which have a high potential of yielding uncertain results [63]. Machine learning (ML) is a subset of AI that primarily serves to help learn patterns from data. Use of ML in drug discovery can significantly speed up and ease processes such as chemical synthesis, target validation, lead discovery, preclinical development and pharmacovigilance studies [64]. ML algorithms, through the analysis of extensive datasets, can uncover intricate patterns and trends that may not be immediately recognized by human scientists. This capability facilitates the discovery of novel bioactive compounds with reduced side effects at a significantly faster rate than classical protocols [63]. In 2020 with the help of AI based Centaur Chemist drug discovery platform Exscientia and Sumitomo Dainippon Pharma were able to develop DSP-118 a new drug candidate intended to treat obsessive-compulsive disorder (OCD) and it took 12 months to start phase I clinical trials, whereas traditional methods of drug discovery would require 4-5 years to reach phase I clinical trials [65]. DSP-118 is a first AI-designed compound and a potent, long-acting 5-HT1A receptor agonist [66]. A compound called ISM01-055, developed by Insilico Medicine to target the NCK-interacting protein kinase TNIK [67] for the treatment of idiopathic pulmonary fibrosis (IPF),

was one of the first AI-designed compounds to enter phase II clinical trials in June 2023 [68]. In a phase I clinical trial among 78 healthy participants ISM01-055 demonstrated comparable safety and pharmacokinetic profiles [67]. Xie et. al (2025) developed TransPharmer, a generative model which uses specific characteristic of pharmacophores, referred to as 'pharmacophore fingerprints' to synthesize new compounds with increased potency [69].

AI can help in generating predictive models for development of nanocarriers such as liposomes, micelles and nanoparticles by incorporating data on biological and physiochemical properties of the carriers and potential drug candidates [70]. The naïve Bayes algorithm can predict interactions of proteins and drugs and facilitate drug repurposing as a result [71]. Currently, deep learning techniques are also used to predict adverse drug reactions (ADRs) such as nausea, vomiting and diarrhea based on changes in gastrointestinal pacemaker activity (GIPA) using the Asian musk shrew (S. murinus) as model capable of vomiting [72].

However, AI is not a perfect and universal solution for drug discovery despite its potential advantages and its use is associated with certain challenges. Since ML heavily relies on availability of large and precise datasets; thus, if the studied data is limited or low in quality the resulting algorithms may become less accurate, less reproducible and less practical [73]. Another concern arises due to potential bias in data sets that may result in exacerbation of healthcare gaps between low-income and high-income countries [74]. Healthcare systems work with sensitive patient data such as medical histories, genetic profiles and other clinical documentation. Another disadvantage is that AI-based technologies can be susceptible to cyber threats and there is a growing need to develop strict security measures to protect sensitive patient data [75]. Furthermore, the application of patient data in training AI algorithms, raises ethical challenges related to informed consent and ownership of the data as patients may not completely understand how their data is being used, or may not have consented for its use in such manner [75]. Aside from data acquisition and safety concerns, there is also an issue of varying representation techniques – a single molecule may be represented by molecular graphs, molecular fingertips and SMILES (Simplified Molecular Input Line Entry System) [76], analyzing all these data together would require sophisticated algorithms as well as specialist capable of understanding the relationship between features of an input and corresponding output properties [77].

Conclusion

Identifying and developing new treatments is a long, complicated and expensive process that relies on extensive research and investment. In more than 90% of cases, chemical entities being studied as potential treatments for existing diseases never make it through the bench to bedside journey and those that do, are most likely modified versions of already existing compounds and may not offer additional health benefits. Current drug discovery efforts are limited due to lack of demonstrated efficacy, inadequate preclinical models, organ toxicity, complex mechanisms of action and financial constraints.

However, incentives and options for conditional authorization provided by regulatory agencies can markedly facilitate and speed up the development of new drugs. It is also evident that the success of drug discovery efforts in the future heavily depends on mutually beneficial collaboration between academic institutions and industry partners. Research collaboration of industry and academia consists of several stages, which may span over years or even decades. On one hand, such long-term collaboration efforts allow to transfer knowledge and innovation, sustain resources and funding in a stable and reliable manner. On the other hand, over time, the goals of academia and industry may diverge, leading to potential misalignments. Furthermore, potential disputes over intellectual property rights for innovative ideas may be one of the factors discouraging academic researchers from participating in such collaboration. Both academia and industry need to be incentivized, albeit for different purposes: the former to conduct clinical trials following the results from preclinical studies, and the latter to invest in developing therapies in areas perceived as less financially favorable.

Since their introduction, various computational methods have been increasingly utilized in drug discovery to automate and enhance the process. The emergent use of AI in drug development holds promise for a more accelerated, refined and precise process. Recent advancements, such as AI-designed molecules (e.g., ISM01-055) entering clinical trials, illustrate AI's growing credibility. However, it still faces many challenges in terms of data acquisition, analysis and safety. While the technology is being refined to provide

reliable outcomes, major challenges such as data storage, diversity and safety need to be addressed to ensure patients' trust and compliance. If integrated effectively, AI could dramatically reduce the timelines and costs of drug discovery. Importantly, it could also reveal potential pitfalls in drug activity and toxicity prior to transitioning to animal studies.

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