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PERSPECTIVE ARTICLE

Revolutionizing new drug discovery: Harnessing AI and machine learning to overcome traditional challenges and accelerate targeted therapies

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Abstract

Designing highly targeted, selective drugs with desirable absorption, distribution, metabolism, excretion, and pharmacokinetic (PK) profiles; single-digit nanomolar efficacy; and a wider therapeutic index are challenging. In the traditional drug discovery process, researchers screen thousands of chemical compounds during pre-clinical development, progressing through hit identification, lead optimization, and candidate selection to shortlist – potential clinical candidates with favorable PK profiles, high tolerability, and manageable toxicity. The selected candidate must demonstrate sufficient efficacy in treating the target disease in humans. Despite these efforts, the success rate of the pre-clinical candidate to sail through Phase I, Phase II, and Phase III in clinical trials remains exceedingly low. Supported by powerful data-driven tools, artificial intelligence (AI) has transformed this traditional drug discovery process by enabling the analysis of large quantities of omics, phenotypic, and expression data to identify the biological mechanisms of pathological conditions and in turn identify druggable proteins or genes. The generative AI-powered toolbox creates novel compounds from scratch, assists scientists in optimizing druggability attributes, and bridges the differences between animal and human physiology and anatomy to predict potential toxicity in humans with high accuracy. This review discusses the bottlenecks in the traditional drug discovery approach, the impact of AI and machine learning (ML) in drug discovery, and potential challenges associated with AI/ML adoption.

Keywords: Novel chemical entity; Absorption, distribution, metabolism, and excretion; Pharmacokinetics; Artificial intelligence; Machine learning; Deep learning; Generative AI; Drug discovery and development

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1. Introduction

Artificial intelligence (AI) has revolutionized drug discovery and development by identifying novel targets, predicting drug–target interactions with high accuracy, designing compounds from scratch, facilitating *in silico* pharmacokinetic (PK) and pharmacodynamic analyses, and optimizing drug formulations for the intended route of administration. AI-assisted prediction of the physiochemical properties, bioactivity, binding affinity, and multitarget effects of new chemical entities (NCEs) is greatly benefiting drug discovery companies, enabling them to anticipate druggability attributes

and prioritize compounds for wet-laboratory profiling accordingly. As a result, the chemical synthesis of novel moieties for wet-laboratory evaluation has been reduced to one-tenth of the previous workload. AI predictive tools are also helping researchers identify potentially unsuitable molecules early in the pre-clinical stage, allowing them to "fail fast" and save both time and resources. This revolutionary AI approach has not only impacted the discovery and pre-clinical development of new drugs but has also refined clinical trials through improved patient selection and stratification, generation of early safety and tolerability warning signals, and real-time collation of multicentric clinical trial data, thereby increasing success rates. AI has further facilitated the generation of clinical trial procedures and reports, helping clinicians draw meaningful insights from the vast data produced during multicentric trials. This mini-review briefly discusses the conventional drug discovery and pre-clinical development process, setbacks associated with traditional methods, and how AI is bridging these gaps to accelerate new drug development. Furthermore, it explores the challenges and limitations associated with the implementation of AI in both pre-clinical and clinical settings.

2. Drug discovery and development

Drug discovery and development is a challenging, lengthy, and costly process. The time taken for a drug to move from the wet-laboratory stage to market is approximately 10 – 12 years, with costs ranging from $161 million to $4.54 billion.[1]

Despite the investment of billions of dollars, significant efforts, and resources, nearly nine out of 10 potential drug candidates fail in clinical trials,[2] and only one progresses from bench to bedside. The Center for Drug Evaluation and Research (CDER-USFDA) approved 50 new drugs in 2021, 37 in 2022, 55 in 2023, and 22 (as of this writing) in 2024. For NCEs entering first-in-human trials, the failure rate remains high: around 80% in the cardiovascular segment, 84% in arthritis pain and infectious diseases, and 92 – 95% in oncology and central nervous system therapeutics. Some reasons for the high attrition rate in clinical trials include off-target toxic side effects/unmanageable toxicity, poor PK properties, and suboptimal clinical efficacy.[3] Figure 1 shows the various stages of classical drug discovery and the pre-clinical development flow.

More focused efforts are now being made to develop methods and approaches that accelerate the drug discovery process, reduce research and development costs, and increase the success rate of clinical candidates. Assay miniaturization technologies and the availability of highly selective, sensitive analytical instruments have shaped next-generation drug discovery.[4] *In silico* absorption, distribution, metabolism, and excretion (ADME) screening, combined with cost-effective and less labor-intensive *in vitro* studies, is being adopted in early drug discovery to selectively eliminate compounds with poor ADME and PK attributes.[5]

Innovative approaches are being used to design targeted chemical libraries or fine-tune the ADME profile of NCEs transitioning into lead optimization to reduce late-stage attrition rates.[6] In addition, developing *in vitro* model systems that resemble or closely mimic human tissues or organs to predict acute drug toxicity or establish a PK/PD relationship to reduce clinical-stage failures is becoming a trend.[7,8] The USFDA recently accepted pre-clinical efficacy results from human organ-on-a-chip models and approved the clinical trial IND application for the mAb sutimlimab, manufactured by Sanofi.

2.1. Drug safety and toxicity

Drug safety and toxicity evaluation, spanning both pre-clinical and clinical trials, is a crucial step in drug discovery and development. Its aim is to identify and assess any potential side effects or adverse responses to the drug. Pre-clinical safety evaluations primarily rely on animal testing in rodent and non-rodent species, with variations in duration, design, and objectives. These studies include general toxicity, reproductive and developmental toxicity, carcinogenicity, immunotoxicity, and functional evaluations of key organ systems, such as the respiratory, central nervous, and cardiovascular systems. Identification of possible toxicity in humans, characterization of the toxicity (morphology, dose-response, reversibility, etc.), and assessment of whether it can be effectively monitored and managed in human clinical trials are the main objectives of pre-clinical drug safety assessment research. Pre-clinical studies also produce endpoints commonly used to assess health and disease in humans, such as serum biochemistry, hematology, urinalysis, histopathology, and vital organ function evaluation.

Conventionally, NCEs progress through drug discovery stages until crucial data reveal a low safety margin (therapeutic index), suboptimal efficacy at clinically relevant doses, or an undesirable PK profile. If the pre-clinical data are unconvincing, further development of the NCE is halted, and sometimes, the entire program for that target is abandoned. This causes significant setbacks, resulting in considerable losses of time, resources, and money. For selected candidates, drug safety and tolerability present major clinical challenges, with safety concerns accounting for 35% of Phase I failures and 28% of Phase II failures.

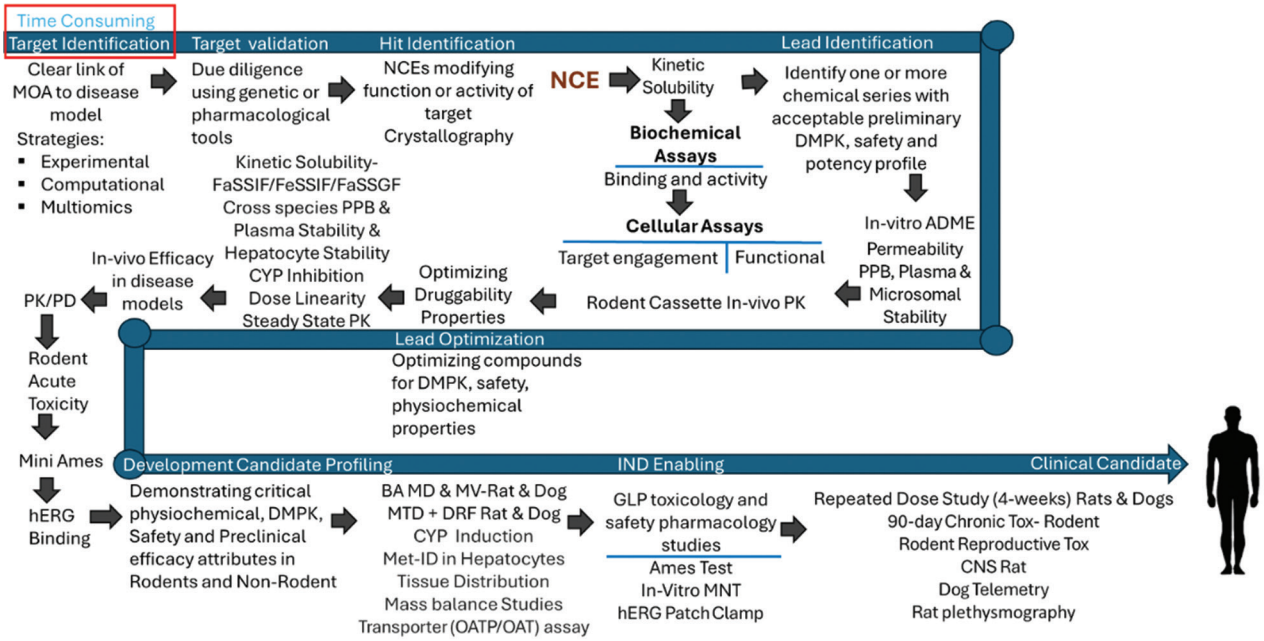

Figure 1. Classical drug discovery and pre-clinical development flow
Abbreviations: MOA: Mechanism of action; NCE: New chemical entity; DMPK: Drug metabolism and pharmacokinetics; ADME: Absorption, distribution, metabolism, and excretion; CYP: Cytochrome P450; PD: Pharmacodynamics; PPB: Plasma protein binding; BA: Bioanalytical; MD: Method development; MV: Method validation; GLP: Good laboratory practice; MTD: Maximum tolerable dose; DRF: Dose range finding; hERG: human Ether-à-go-go-related gene; FaSSIF: Fasted state simulated intestinal fluid; FeSSIF: Fed state simulated intestinal fluid; FaSSGF: Fasted state simulated gastric fluid.

2.2. Toxicity-driven phase IV withdrawals

Unexpected toxicity is the primary reason for drug dropouts not only during clinical trials but also in post-marketing [Phase IV] withdrawals. It is nearly impossible to predict drug safety and toxicity with confidence even in late-stage development, as rare adverse events often appear only after the drug has been administered to a large global population with diverse medical histories. Toxicity-related drug failures account for two-thirds of post-market withdrawals.[9]

For instance, aprotinin (Trasylol) was withdrawn due to increased risk of death, Tegaserod (Zelnorm) due to heightened risk of heart attack and stroke, pergolide mesylate (Permax) due to severe heart valve damage, ximelagatran (Exanta), and pemoline (Cylert) due to their hepatotoxicity, and rofecoxib (Vioxx) as it led to myocardial infarction as a toxic effect.

In the United States, drug toxicity is the leading cause of acute hepatotoxicity, with over half of acute liver failures caused by idiosyncratic drug-induced liver injury (iDILI).[10] It is possible for iDILI to go unnoticed even in large phase III trials.

2.3. Drug-induced liver injury (DILI)

DILI is among the most unpredictable adverse reactions to xenobiotics in humans, causing hepatotoxicity, liver necrosis, and alterations in hepatic enzyme levels.[11-14] It is the leading cause of post-market withdrawals of approved drugs such as troglitazone, tolcapone, trovafloxacin, bromfenac, nefazodone, ximelagatran, lumiracoxib, and sitaxentan. Acetaminophen is the second-most frequent cause of acute liver injury and hepatic failure worldwide, often requiring liver transplantation. Marketed antibiotics – amoxicillin-clavulanate, trimethoprim, and erythromycin – also contribute to the list of hepatotoxic drugs.

NCEs, or withdrawn drugs such as nefazodone and troglitazone, interfere with bile acid homeostasis, which is vital for hepatocyte survival, by inhibiting the bile salt export pump (BSEP), an ATP-binding cassette transporter crucial for maintaining bilirubin and bile salt homeostasis. Inhibition of BSEP is a risk factor for cholestatic DILI, as it can cause accumulation of bile acids in hepatocytes, thereby increasing liver toxicity. In addition, NCEs can directly contribute to liver toxicity by altering the exposure and clearance of drugs that are substrates for efflux transporters. Figure 2 illustrates the metabolic pathway of troglitazone and its metabolites, which leads to cholestasis and liver toxicity.

An example of a toxicity-centric drug discovery strategy involved identifying an active scaffold with single-digit nM *in vitro* potency. *In vivo* studies were then conducted,

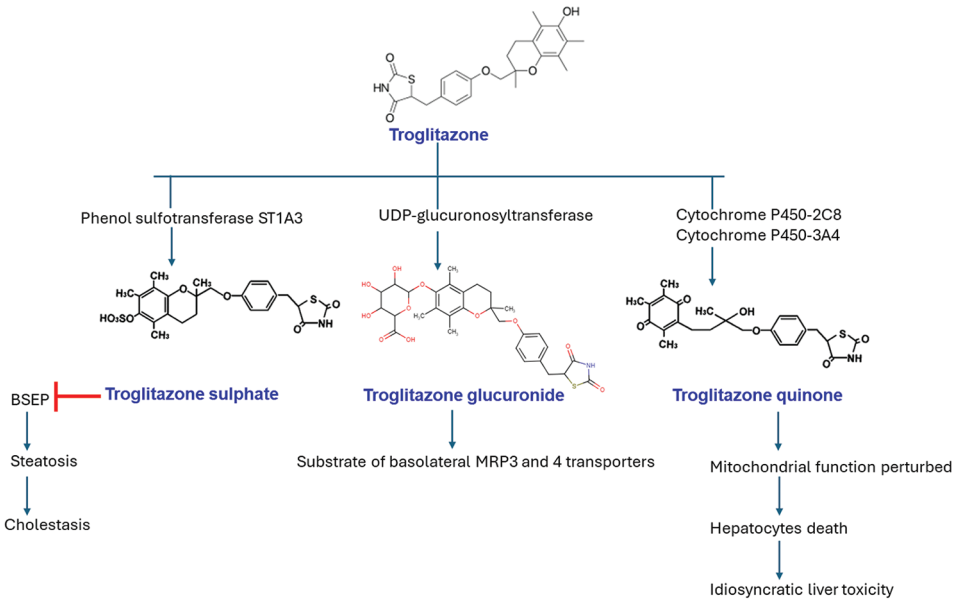

Figure 2. Biotransformation of the peroxisome proliferator-activated receptor gamma agonist "Troglitazone"

including rodent PK, efficacy testing in a rodent disease model, and acute toxicity experiments. If the compound proved effective and was expected to achieve the same efficacy in humans at a total daily dose of ≤100 mg with manageable toxicity, the pre-clinical screening approach for backup/follow-on compounds was reversed. New variants of that scaffold were first subjected to *in vitro* profiling, followed by a mouse cassette PK study.

The *in vivo* toxicity of each variant was assessed, followed by efficacy studies. Widening of the therapeutic index allows for the acceptance of somewhat lower potency.

Figure 3 illustrates the *in vitro* and *in vivo* tests specified by the Organization for Economic Co-operation and Development to assess the genotoxicity, mutagenicity, and organ-specific toxicity of NCEs as well as the corresponding AI/machine learning (ML) tools for *in silico* prediction.

2.4. Drug toxicity effect translation from animals to humans

However, toxicological data derived from animal models align with human outcomes in only 63% of cases when extrapolated from non-rodents and 43% from rodents and < 30% when predicting adverse drug reactions in humans. In addition, drug-induced neurobehavioral symptoms such as nausea, somnolence, and dizziness, which are common in patients and often lead to intolerance, are poorly predicted by animal studies using conventional endpoints.[15] Approximately 90% of drug candidates fail, largely because animal studies cannot reliably predict efficacy, safety, and human responses due to species differences.[16] These translational limitations have heightened concerns that animal studies may mislead us, contributing to clinical candidate failures. It is also important to note that selecting the appropriate non-rodent species for pre-clinical evaluation plays a key role in the clinical success of NCEs. For example, in evaluating a new oral drug with an extended or sustained-release formulation, minipigs may provide more relevant data than beagle dogs. This is because pigs more closely resemble humans than beagle dogs in terms of gut anatomy (intestinal length per kilogram of body weight), physiology, bacterial gut colonization, skin architecture, and body fat distribution.[17]

2.5. Animal testing alternatives

The USFDA Modernization Act 2.0 allows for alternatives to animal testing, enabling the use of pre-clinical assays that utilize organ-on-chip platforms, organoids, and 3D spheroid cultures of human origin to better predict potential toxicities in humans. Recently, the USFDA favorably considered pre-clinical efficacy results from human organ-on-chip research, alongside existing safety data, to approve the clinical trial IND application of sutimlimab developed by Sanofi.

Notably, primary cultures of cells derived from the human heart, liver, or kidney can display differentiated functions, in addition to toxicity markers, and mimic responses observed in intact tissues. However, the challenge of maintaining a normal gene expression profile and dynamic biochemical responses to varying drug concentrations remains unresolved.

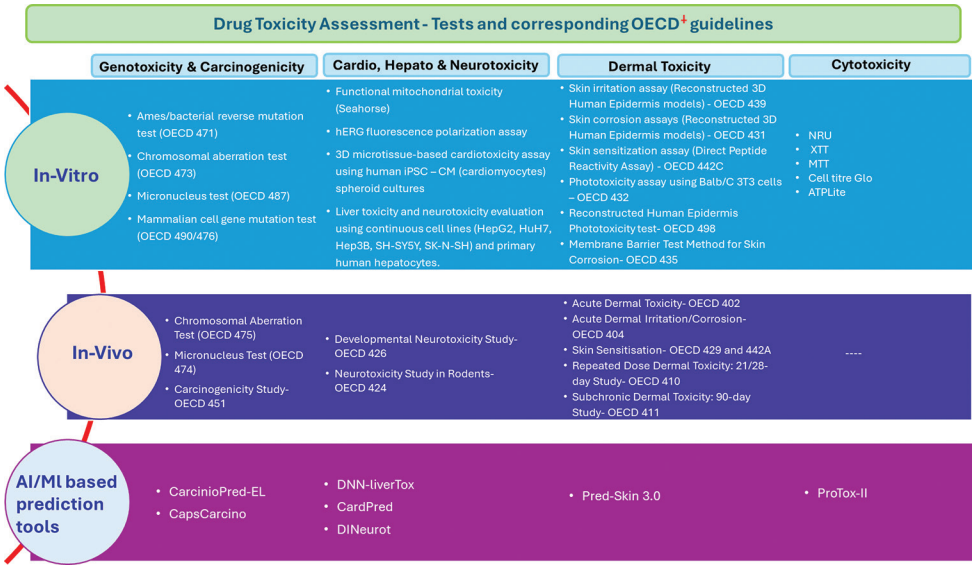

Figure 3. Drug toxicity evaluation: wet-laboratory experiments and artificial intelligence/machine learning-based *in silico* prediction tools
Abbreviation: OECD: Organization for Economic Co-operation and Development.

Bridging the gap between static *in vitro* models and dynamic *in vivo* homeostatic systems is difficult. Furthermore, these models need to undergo extensive validation to demonstrate limited interexperiment and inter-laboratory variability as well as reproducibility in *in vitro in vivo* correlation. Therefore, these models are currently used for exploratory toxicology and establishing PK/PD relationships.

For *in silico* predictions, knowledge-based standalone quantitative structure-activity relationship tools have long been available. Examples include Derek, Meteor, StAR, and TopKat for drug toxicity, Ecosar for ecotoxicity, and Biowin for biodegradability prediction. However, traditional approaches based on structure-activity relationships and physicochemical attributes did not account for drug interactions with the human-specific liver proteome, resulting in inaccurate predictions of DILI.[18] Over the past decade, it has become clear that integrating various drug discovery verticals into a unified computational tool is essential to lowering attrition rates and shortening the drug discovery timeline. AI/ML models that combine physicochemical attributes, anticipated on-target biological interactions, and predicted off-target toxicity in humans can help address gaps in predicting DILI.

Recently, there has been a parallel emphasis on AI/ML-based approaches to accelerate the drug discovery process and reduce NCE failures during clinical trials and phase IV withdrawals of marketed drugs.

3. New drug discovery in the AL/ML era

Over recent years, numerous AI/ML approaches have been developed and successfully implemented at various stages of drug discovery and development, from hit identification to candidate selection for clinical trials.

During the lead discovery phase, AI models such as recurrent neural networks and generative adversarial networks generate NCEs, predict target binding affinities, and expedite candidate selection. Molecular dynamic simulations and ML approaches enhance the efficiency and accuracy of *de novo* drug design.

Compounds predicted to have poor *in vitro* ADME (solubility, permeability, chemical, and metabolic stability), suboptimal PK properties (low oral bioavailability), drug–drug interaction (DDI) potential (CYP inhibition or induction), and toxicity (mechanism/off-target) that could affect the clinical safety and efficacy of NCEs are effectively identified and circumvented by AI/ML-powered virtual strategic planning platforms.[19,20] Consequently, the holistic AI/ML-driven evaluation across all drug discovery verticals facilitates early no-go decisions.[21,22] Figure 4 outlines the brief history of AI-driven drug discovery beginning - 2017 – 2018.

3.1. AI

AI, a branch of computational science, focuses on creating systems that perform tasks typically requiring human intelligence. In drug discovery, AI has been successfully applied to target protein structure identification,[23,24] *de novo* drug design,[25,26] compound docking studies,[27] virtual screening,[28,29] retrosynthesis reaction prediction,[30,31] bioactivity and toxicity prediction,[32,33] and *in silico* clinical trials.[34] Figure 5 illustrates AI, its subsets, and respective tools.

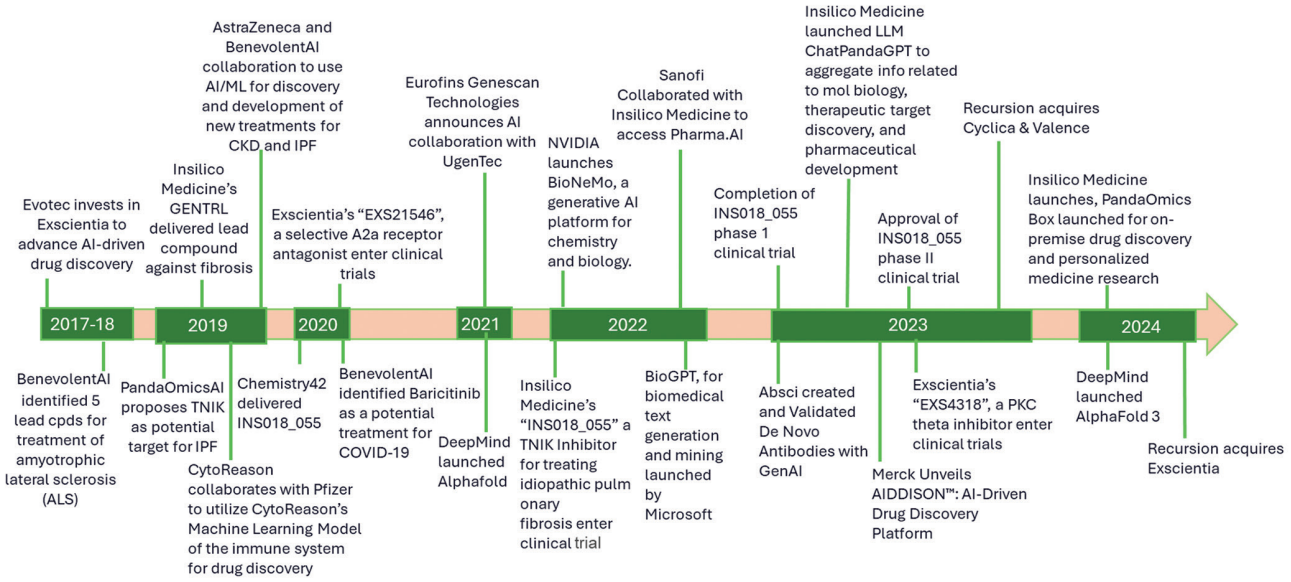

Figure 4. A brief history of artificial intelligence-driven drug discovery beginning 2017 – 2018

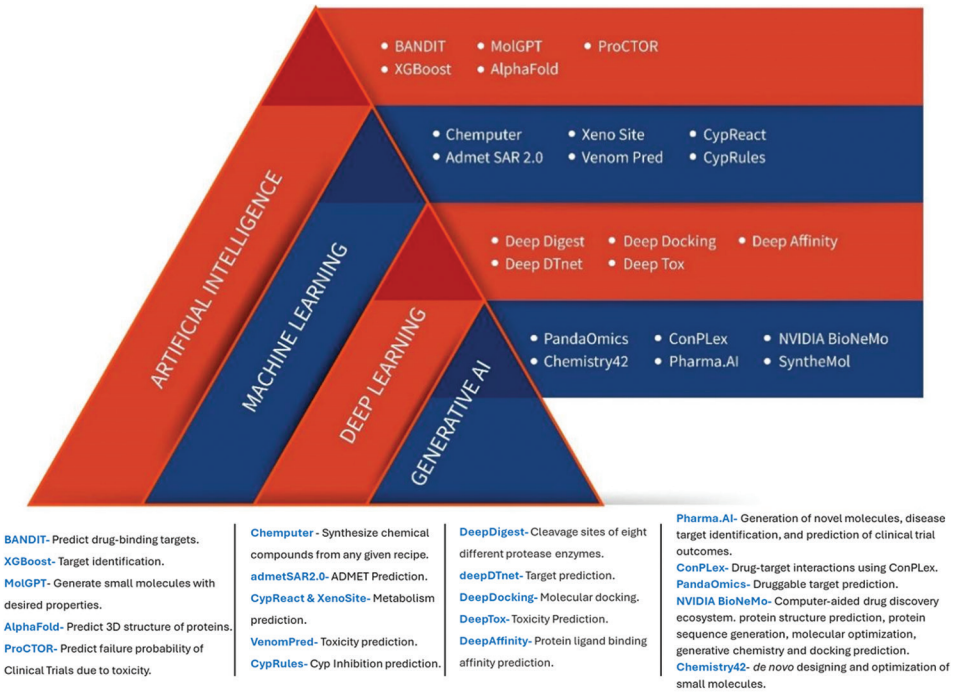

Figure 5. Artificial intelligence, its subsets, and respective tools

Next-generation AI/ML tools, such as AIDDISON, PREDICT, MANTRA, RoseTTAfold, ESMFold, OpenFold, ProGen, ProteinMPNN, EvoDiff, RFdiffusion, BioGPT, chatPandaGPT, enhance data quality and prediction accuracy by integrating PK profiles, DDI, off-target toxicity, chemical scaffold-driven toxicity, animal toxicity versus human primary culture toxicity, and geographical ethnicity differences in patient population response (driven by physiological, genetic, and environmental factors) to administered NCEs.[24,35,36] Molecular docking tools, such as AutoDock 4, AutoDock Vina, DiffDock, Deep Docking, and DL-DockVS, dock a single ligand by evaluating different poses and atoms in parallel, reducing computational analysis time.[37,38]

Figure 6 illustrates AI/ML-powered drug discovery and development workflow.

AlphaFold2, for instance, presents new prospects for structure-based drug discovery, particularly for proteins with unverified structures.[39] However, AlphaFold2 data can be difficult to interpret, and its output in virtual screening has shown inconsistent results when protein folding and dynamic conformational changes are not taken into account.[40] Although AlphaFold2 performs well in the domain of structure prediction, it falls short in addressing conformational dynamics[41] and multimeric structure prediction.

Figure 6. Artificial intelligence/machine learning-driven drug discovery workflow

An improved version, "AlphaFold3," codeveloped by Google DeepMind and Isomorphic, was released in May 2024. AlphaFold3 can predict the nature of protein–molecule interactions far more effectively than AlphaFold2. While AlphaFold2 is primarily focused on predicting protein structures, AlphaFold 3 extends its capabilities to predict interactions between proteins and a wider range of molecules, including DNA, RNA, and small-molecule ligands. Figure 7 lists several examples of AI-assisted and generative AI (GenAI)-driven drugs.

3.2. AI-driven drug toxicity prediction

Optimizing the chemical structures of NCEs to enhance their biological activities while ensuring suitable safety profiles (such as low *in vitro* and *in vivo* toxicity) is challenging. Newly designed molecules will be less toxic only if their physicochemical characteristics and potential off-target effects are considered alongside their biological activity in a dynamic setting.

The availability of big data and open-access toxicological datasets has made toxicity prediction feasible.[42] For example, the chemoinformatic platform "ChemTunes•ToxGPS®" developed by Molecular Networks and Altamira integrates multiple databases, including physicochemical parameters, xenobiotic metabolism, toxicokinetics, and the ToxCast/Tox21 database, to support the safety and risk assessment of chemical substances. Figure 8 illustrates the role of ML in drug toxicity prediction.

The discontinuation of the first two AI-designed clinical candidates (Exscientia's cancer drug EXS-21546

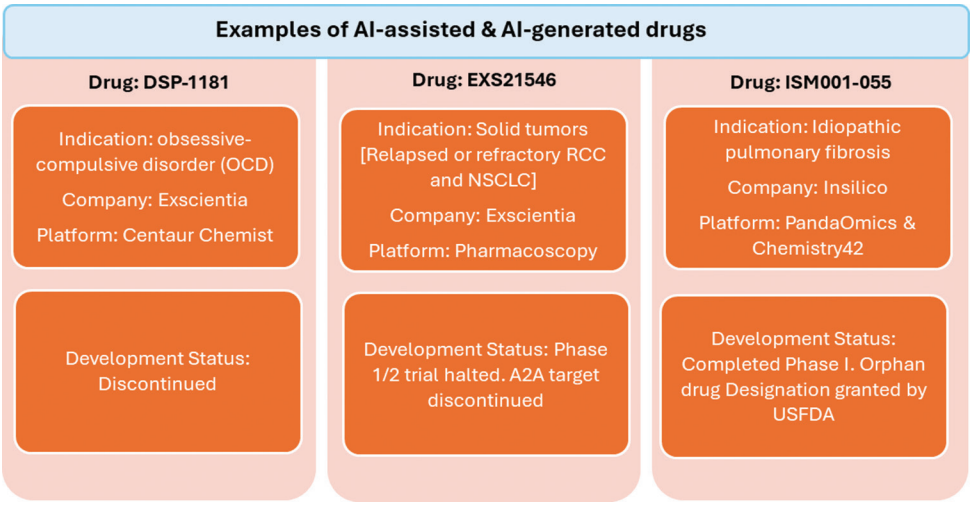

Figure 7. Examples of artificial intelligence-assisted and GenAI drugs
Abbreviations: A2A: Adenosine A2a receptor antagonist; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; USFDA: United States Food and Drug Administration.

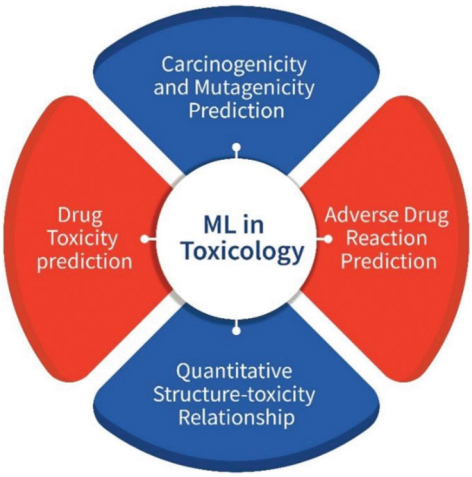

Figure 8. Role of machine learning in drug toxicity prediction

and BenevolentAI's dermatitis drug BEN-2293) was a setback. However, BenevolentAI's repurposed drug Olumiant (baricitinib, a rheumatoid arthritis therapy) was approved by the US FDA in May 2022 for the treatment of COVID-19.

3.3. ML

ML, a subfield of AI, uses defined datasets to create algorithms for developing predictive and descriptive models, which are useful for analyzing data, drawing insights, and making informed decisions. There are two types of ML models based on the data used to generate an algorithm: Supervised and unsupervised. Supervised ML models are trained with labeled input data and a defined outcome, whereas unsupervised ML models use raw input data to find relevant patterns and relationships without prior knowledge.

In recent years, ML has become a powerful tool in drug discovery, transforming the way we investigate and understand large, complex information about drug behavior in biological systems. ML predicts novel drug–target interactions with reasonable accuracy.[43] Clinical trial datasets have been used to build ML models that forecast trial success early, thereby reducing unrecoverable costs and saving time.

Large language models (LLMs), a component of AI's natural language processing that overlaps with ML, are gaining importance and popularity. By drawing scientifically valid conclusions from large datasets, such as genomic, proteomic, and metabolomic data, and existing literature, LLMs help researchers generate hypotheses and make sense of voluminous experimental data. LLMs effectively analyze large biological datasets to predict new druggable targets that conventional approaches may miss. Furthermore, LLMs assist in drug repositioning and repurposing.

3.4. Deep learning (DL)

DL, a subbranch of ML, learns from algorithms and their outcome data to further improve using neural networks.[44] This disruptive technology has been effectively applied in various complex scenarios. For instance, NCEs may have weak interaction strengths but be highly target-selective, meaning they exhibit strong target selectivity but relatively low absolute potency. In these cases, the goal is to balance NCE potency and selectivity, finding the most selective molecule with the minimum desirable potency. Tools such as Affinity2Vec, DeepDTA, and DeepGS can predict drug–target binding affinity, assign binding affinity scores, and rank compounds.[45-47]

One approach to improving a ligand's druggability during the lead optimization phase is to expand it by adding a single chemical group (fragment). Fragment-based drug design, on the other hand, involves adding multiple fragments. Geometric DL helps expand the ligand by identifying the site(s) on the ligand to add fragments, suggesting the most suitable fragments, and predicting the geometry of the added fragments.[48]

Furthermore, DL tools predict chemical toxicity by comparing millions of known substances based on biological mechanisms or physicochemical features. DL algorithms trained on datasets of well-known medications can accurately forecast the activity of NCEs.[49]

3.5. GenAI

GenAI, a subset of DL, creates new content based on learned information. As one of the most advanced forms of AI, GenAI can generate new molecules from training data. To develop novel molecules for specific applications or predict their behavior in biological environments (e.g., receptor binding), algorithms are trained on the chemical–physical features and 3D forms of molecules.

GenAI, coupled with data analytics, can design structures with optimal druggability attributes and predict their physicochemical properties, drug–target interactions, potency, efficacy, and toxicity with reasonable accuracy. It also aids in designing the most suitable drug formulation and delivery system, which improves stability and oral bioavailability. In addition, GenAI can reduce the time required for regulatory dossier submissions. During clinical evaluation, GenAI assists in drafting the best-fit clinical trial design and patient recruitment strategies. AI tools help identify novel biomarkers and surrogate endpoints to predict patient responses to treatment. Furthermore, GenAI can infer safety and tolerability signals for early intervention, improving clinical trial success rates.

Leveraging GenAI for drug discovery and pre-clinical development, *in silico* medicine identified a molecule target, generated novel drugs, assessed target binding and pre-clinical efficacy, and predicted clinical outcomes for lead candidates. Following pivotal pre-clinical studies, "INS018_055" was selected and is now in phase IIa clinical trials. Just 18 months after the project began, in February 2021, the pre-clinical candidate was chosen. Insilico's Biology42: PandaOmics and Chemistry42 – generative chemistry platforms were used to create INS018_055 for treating idiopathic pulmonary fibrosis. It was developed from scratch in just 3 weeks, with another 3 weeks to validate the compound for treating fibrosis.[50] This process would have taken at least 2 years if it had followed the traditional discovery route. Further, to reach clinical evaluation, it would have taken >$400 million and up to 6 years for NCE if pursued through traditional drug discovery methods. These milestones were achieved by *in silico* medicine in a third of the time and at a tenth of the expense.

4. Small but significant challenges

Developing AI/ML tools is cost-intensive, with a significant portion of drug development expenses allocated to clinical trials. Although the cost and duration of clinical trials may remain unchanged with AI/ML, these technologies greatly facilitate the customization of clinical trial protocols, patient selection, stratification and retention, real-time clinical data analysis, and forecasting of safety and efficacy trends. Thus, investing significant time, money, and resources in creating these tools is expected to meaningfully reduce the bench-to-bedside timespan and cost.

However, the advanced coding and programming skills required for AI/ML tool creation make it challenging for many small and mid-size pharma R&Ds to develop these tools in-house. Consequently, they often rely on in-licensing tools from software tech giants or partnering with them to access AI/ML tools. Using AI/ML tools from software tech companies under non-exclusive agreements carries risks of intellectual property loss or data breaches unless they are operated on-premises, such as with "PandaOmics Box."[36]

With the advent of AI and ML, NCEs are designed *in silico*, and their physiochemical characteristics, PK parameters, *in vitro* and *in vivo* efficacy, and toxicity properties are predicted using advanced computational algorithms. From an initial selection of 50 – 100 molecules, only 5 – 10% that meet the highly desirable predicted parameters are subjected to wet-laboratory profiling. This approach significantly reduces animal usage and eliminates the chances of serendipitous drug discovery. Therefore, the discovery of molecules such as penicillin, warfarin, cisplatin, lysergic acid diethylamide, meprobamate, and chlorpromazine is no longer expected. Notably, a study published in 2012 indicated that 24% of all marketed drugs and 35% of anticancer drugs have originated from serendipitous discoveries.[51]

The success of AI depends on data. Large datasets are essential for effectively training AI-driven approaches. Unfortunately, data are sometimes limited, low in quality, inconsistent, or biased, compromising the reliability and accuracy of the findings.

GenAI models trained on skewed or partial data or on prior trials of similar medications will reflect these biases in their results. While GenAI algorithms can explore and develop unique chemical structures previously unexplored by human researchers, they will produce only similar chemotypes (me-too moieties) if trained on datasets primarily consisting of one type of molecular property. Consequently, they will be unable to generate results in underrepresented chemical spaces, which are vast and multidimensional.

To build a robust and dependable AI platform for *in silico* drug discovery, AI systems should be trained on the entire drug evolution process, from hit identification to lead optimization, clinical candidate selection, and market authorization, rather than solely on approved marketed products. However, a significant portion of historical data from various discovery programs is privately owned by innovators. The drug discovery and development data available in the public domain are stored in silos and have not been properly connected or integrated. Many AI businesses are grappling with massive amounts of disconnected data spread across too many verticals, leaving them to learn by doing.

Occasionally, AI-driven *in silico* drug development initiatives produce molecules with structures that are challenging for medicinal chemists to synthesize in reality. Combining GenAI with conventional experimental techniques will enhance the drug development process, making it faster and more affordable while generating more effective and customized candidate molecules. However, modern AI-based approaches cannot completely replace traditional experimental techniques as well as the invaluable knowledge and experience of human researchers.[52] A recent report revealed that the success rate of AI-derived molecules is 80 – 90% in phase I trials but drops to approximately 40% in phase II trials.[53] GenAI can only make predictions based on currently accessible data, and experienced human drug hunters are still needed for result validation and interpretation. Thus, GenAI alone may not be reliable in aspects that directly affect people's health. Nevertheless, there is an opportunity to expedite

the entire process of finding novel drugs and accelerating pre-clinical and clinical developments by combining the predictive powers of GenAI with the knowledge and experience of human researchers.

5. Conclusion

AI, in particular GenAI, is navigating drug hunters in the development of new therapeutics and emerged as a proficient alternative tool to the traditional drug discovery approach. The advanced AI/ML/DL transformative tools are expediting drug discovery by assisting target identification, computational chemistry, predicting drug–target interactions, facilitating *in-silico* pharmacology analysis, and evaluating off-target toxicity. Based on AI/ML readouts, the compounds can be prioritized for wet-laboratory profiling, thus reducing the cost and time of pre-clinical drug development. AI/ML-driven approaches have been leveraged for designing clinical prototype formulation and also revolutionizing clinical trials by better patient selection, predicting safety and tolerability signals for early action, and improving the clinical trial success rate.

Furthermore, AI/ML tools are being effectively utilized for generating clinical trial study protocols, comprehensive reports, and drawing meaningful conclusions out of the voluminous data generated during multicentric clinical trials. We may witness AI-generated drugs hitting the market sooner than later.

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Conflict of interest

Satinder Singh and Pratima Srivastava are employees in DMPK, Aragen Life Sciences Limited, Hyderabad, India. The other author declares no conflict of interest. The authors declare that they have no competing interests.

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Conceptualization: Satinder Singh
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Writing–original draft: Satinder Singh
Writing–review & editing: Satinder Singh, Pratima Srivastava

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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