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Review Article

Redefining Preclinical Research Paradigms: AI-Driven Drug Discovery as a Transformative Approach to Accelerate Innovation, Improve Predictive Accuracy, and Reduce Reliance on Animal Testing

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Abstract

Drug discovery has historically been hindered by extended timelines, high costs, and low clinical success rates. Conventional methods such as high-throughput screening, structure-based design, and medicinal chemistry optimization, while scientifically valuable, often fail to deliver efficient translation into safe and effective therapeutics. Artificial intelligence (AI) and machine learning (ML) now provide unprecedented opportunities to accelerate every stage of drug discovery by leveraging large, heterogeneous datasets and powerful predictive algorithms. This manuscript presents a comprehensive review of AI-driven drug discovery, highlighting advances made between 2019 and 2024. Applications are critically examined across the pipeline: target identification, hit discovery, lead optimization, ADME-toxicity prediction, and clinical trial design. Special emphasis is given to transformative model architectures such as graph neural networks (GNNs), transformer models, and generative frameworks, as well as classical machine learning methods that remain relevant for specific tasks. Challenges including data quality, interpretability, regulatory acceptance, and ethical considerations are evaluated alongside strategies to mitigate bias and improve transparency. Case studies such as DiffDock for generative molecular docking, Trial Pathfinder for AI-based patient stratification, and Mol-BERT for chemical representation learning illustrate the tangible impact of these innovations. The manuscript concludes by identifying research gaps and future directions, including explainable AI (XAI), multimodal data integration, federated learning, and democratization of AI tools for global accessibility. Overall, AI is not simply a set of computational tools but a paradigm shift, offering a faster, more precise, and ethically responsible framework for pharmaceutical research and development.

Keywords: Artificial intelligence (AI); Machine learning (ML); Drug discovery; Target identification; Lead optimization; Graph neural networks (GNNs); Transformer models; Generative AI; ADMET prediction; Clinical trial design; Drug repurposing; Ethical considerations; Explainable AI (XAI).

1. Introduction:

The discovery and development of novel therapeutics is a cornerstone of modern medicine, yet the traditional pipeline remains fraught with inefficiencies. A new drug typically requires over a decade of research and development, with costs frequently surpassing two billion U.S. dollars.[1,2] Even with such investments, attrition rates are alarming—only about 10% of candidates that reach clinical trials ultimately gain regulatory approval. The reasons are multifaceted: lack of efficacy in humans despite promising preclinical results, unforeseen toxicities, suboptimal pharmacokinetic properties, and challenges in identifying appropriate patient subgroups.[3] High-throughput screening (HTS), one of the most widely employed methods, often yields hit rates as low as 2–3%, resulting in vast amounts of wasted resources.[4] Here is a detailed academic-style introduction that expands specifically on the theme of AI-driven drug discovery as a strategy to reduce reliance on animal studies, building upon but distinct from the text you provided.[5,6]

For decades, animal models have been regarded as the "**gold standard**" for evaluating pharmacokinetics, pharmacodynamics, safety, and toxicity before advancing compounds into human trials. Yet, despite their widespread use, animal studies are increasingly criticized on scientific, ethical, and regulatory grounds. From a scientific standpoint, interspecies differences often limit the predictive validity of animal models. Drugs that demonstrate safety and efficacy in rodents, non-human primates, or other model organisms may still fail in human clinical trials.[7] This translational gap contributes to the staggering attrition rates observed in pharmaceutical pipelines, where the majority of

candidates identified as promising in animal models ultimately do not succeed in human testing. From an ethical perspective, the use of animals raises concerns that resonate strongly with the principles of the 3Rs—Replacement, Reduction, and Refinement—which aim to minimize harm and promote alternatives.[8,9,10]

Simultaneously, the regulatory environment is gradually shifting. Several jurisdictions, including the European Union, India, and the United States, have strengthened guidelines encouraging non-animal-based approaches in early drug development. The U.S. Food and Drug Administration Modernization Act 2.0 (2022) marked a significant milestone, formally recognizing non-animal methodologies such as computational models, organ-on-chip platforms, and other *in silico* tools as valid alternatives to animal testing for preclinical evaluation. These shifts reflect a growing consensus that to enhance both predictive accuracy and ethical responsibility, the pharmaceutical industry requires transformative innovations beyond traditional models. Among the emerging technologies, artificial intelligence (AI) and machine learning (ML) represent a particularly powerful set of tools poised to accelerate this transition.[11]

In this context, artificial intelligence (AI) and machine learning (ML) have emerged as disruptive forces. These technologies promise to transform the discovery pipeline by reducing reliance on trial-and-error approaches, improving predictive accuracy, and uncovering patterns hidden within massive datasets that surpass human analytical capacity. The pharmaceutical industry has invested heavily in AI initiatives, with both start-ups and established companies reporting breakthroughs in target discovery, structure-based design, and drug repurposing. Academic research has paralleled this momentum, producing innovative model architectures and benchmarks.[12]

The Role of AI in Rethinking Preclinical Research

Artificial intelligence, encompassing subfields such as machine learning, deep learning, and natural language processing, has already demonstrated transformative potential in optimizing nearly every stage of drug discovery. What is particularly noteworthy is its capacity to provide computationally driven predictions of drug behaviour in ways previously only approximated through animal studies. For example, predictive models of drug toxicity, metabolism, and target engagement are becoming increasingly sophisticated.[13] AI can now simulate complex biological responses by leveraging vast, multimodal datasets from genomics, transcriptomics, proteomics, metabolomics, and clinical data repositories. These predictive insights enable researchers to flag liabilities, forecast pharmacokinetic outcomes, and even model adverse reactions in silico before moving compounds into costly and ethically burdensome *in vivo* studies.

Unlike animal models, which are constrained by species-specific biology, AI systems learn directly from human-relevant data sources, including real-world evidence and patient-derived datasets.[14,15] Such approaches potentially mitigate interspecies translation failures, offering higher external validity when anticipating clinical success. For instance, deep learning algorithms trained on human toxicogenomic datasets can predict organ-specific drug toxicity with a precision rivalling traditional animal-based toxicology study. Similarly, graph neural networks (GNNs) and transformer architectures, adapted to chemical informatics, allow unprecedented accuracy in molecular property predictions, further reducing the reliance on *in vivo* validation.[16,17]

Emergence of In Silico Models as Animal Alternatives

Advances in AI have also accelerated the convergence between computational modelling and experimental innovations such as organoids, organ-on-a-chip platforms, and multi-omics integration. These hybrid models reduce the need for animal experimentation by supplying datasets that can be fed into machine-learning pipelines to refine their predictive performance. For example, microfluidic liver-on-chip devices combined with AI-enabled image analysis create a high-throughput framework for detecting hepatotoxicity earlier than conventional rodent assays. Similar systems are being developed for cardiotoxicity, neurotoxicity, and renal safety. By enhancing the fidelity of human-relevant models, AI not only reduces but, in some cases, may entirely replace specific categories of animal study.[18]

Furthermore, in silico clinical trials, powered by AI and computational biology, are gaining attention as legitimate frameworks to approximate population-level drug responses without involving animal surrogates. Virtual patient cohorts can be modelled using machine learning to capture variability in age, sex, genetics, comorbidities, and polypharmacy. These simulations can forecast heterogeneous treatment responses, guide dose selection, and optimize trial design—all functions that previously required extensive preclinical animal experimentation.[19]

Ethical and Societal Drivers of Change

Reducing the reliance on animal testing is not merely a technological ambition but also a response to shifting ethical and societal priorities. Public opposition to animal experimentation is rising, and consumer-driven industries such as cosmetics have already witnessed large-scale bans on animal testing worldwide. The pharmaceutical sector, though long reliant on animal studies due to regulatory mandates, is now being compelled to align with these ethical imperatives. AI-driven alternatives meet this demand by delivering *data-rich, human-centric models* that promise not only compliance with the 3Rs but also improved translational accuracy. This ethical-technological synergy underpins much of the current momentum toward reformulation of drug discovery pipelines.[20]

Challenges in Implementation

Despite enormous promise, the integration of AI into drug discovery as a direct alternative to animal testing faces several challenges. First, issues of data availability and quality remain paramount. High-performing AI models require large, curated datasets that are often

fragmented, proprietary, or noisily labelled. Toxicology data, in particular, are still heavily reliant on animal-derived datasets, creating potential biases in algorithm training. Second, the interpretability and transparency of AI models pose hurdles for regulatory acceptance. Black-box predictions—even when accurate—struggle to gain regulatory confidence compared to empirically validated animal studies. Third, equity and access concerns persist, as the most advanced AI infrastructures are concentrated in high-resource settings, leaving underfunded labs and low-income regions at risk of exclusion from these scientific advances.[21]

Finally, while AI offers powerful simulation capabilities, rigorous validation protocols will be required before computational models can fully displace animal studies in regulatory toxicology. Ongoing initiatives, such as the OECD's efforts to standardise AI-enabled *in silico* methods, are critical in advancing acceptance within policymaking bodies. Collaboration among academia, industry, and regulators will therefore determine the speed and scope of this transition.[21,22]

Toward a Hybrid and Responsible Future

It is unlikely that animal testing will be fully abolished in the near term. Instead, AI should be conceived as a driver of progressive reduction, wherein computational and predictive methods incrementally displace animal studies across specific stages of drug discovery. Already, compound screening, ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling, and early safety assessments are areas in which machine learning has shown enough promise to significantly reduce *in vivo* workload. As virtual models become increasingly precise, researchers can prioritize only the most promising compounds for limited animal validation, thereby complying with ethical imperatives while also improving pipeline efficiency.[23]

The vision for the coming decade is an AI-augmented drug discovery paradigm where human-relevant data, advanced computing, and predictive analytics form the backbone of preclinical research. In such a system, animals may serve only as confirmatory tools rather than default platforms, marking a profound paradigm shift.[24] Ultimately, this trajectory aligns advances in artificial intelligence with the dual imperatives of scientific innovation and compassionate ethics, offering a future where new medicines reach patients faster, cheaper, and with minimised animal suffering.[24,25]

The central aim of this manuscript is to critically review advances in AI-driven drug discovery between 2019 and 2024, while situating them within broader scientific and ethical frameworks. Specifically, the objectives are:

1. To provide an overview of the evolution of AI applications in drug discovery.

2. To examine methodological frameworks employed in systematic reviews of the field.

3. To analyse specific applications of AI/ML across different stages of the pipeline.

4. To evaluate strengths, weaknesses, and translational challenges of these approaches.

5. To identify research gaps and propose future directions for responsible implementation.[26]

This review distinguishes itself by offering a comparative perspective that juxtaposes modern architectures such as GNNs and transformers against classical ML approaches, while also interrogating persistent issues of data quality, interpretability, and equitable access. By synthesising findings across multiple domains, it aims to guide researchers, industry professionals, and policymakers toward informed decisions on integrating AI into pharmaceutical research and development.[27]

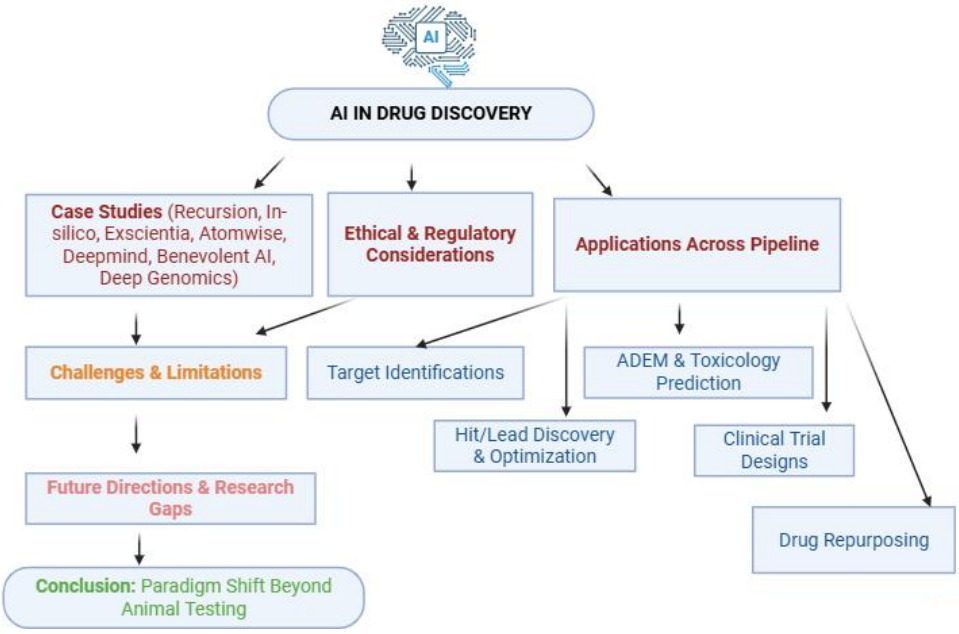

Figure 1: AI in Drug Discovery Flowchart

2. Methods:

2.1 Literature Search Strategy

To construct a rigorous and comprehensive dataset of relevant studies, a systematic search was conducted across multiple academic databases including PubMed, Scopus, Web of Science, and Google Scholar. The search timeframe spanned January 2019 to December 2024, reflecting the most recent advances in the rapidly evolving field of AI-driven drug discovery. Search terms were designed using the PICO framework (Population/Problem, Intervention, Comparison, Outcome), emphasizing keywords such as "artificial intelligence," "machine learning," "deep learning," "graph neural networks," "transformers," "drug discovery," "target identification," "lead optimization," "virtual screening," "drug repurposing," "ADME," "toxicology," and "clinical trial design."[28] Boolean operators and nested phrases were employed to maximise the sensitivity and specificity of results.[29]

2.2 Inclusion and Exclusion Criteria

Table 1: Inclusion and Exclusion Criteria

Criteria Type	Details
Inclusion Criteria	• Peer-reviewed research articles • High-impact reviews and meta-analyses • Studies explicitly focused on AI/ML methodologies in small-molecule drug discovery • Preprints from credible repositories (e.g., arXiv, bioRxiv) if presenting novel and validated insights not yet available in peer-reviewed literature
Exclusion Criteria	• Studies centred on automation, robotics, or formulation science without direct AI integration • Non-English articles • Publications lacking empirical data (e.g., editorials, opinion pieces) • Preprints without novel or validated contributions[30]

2.3 Study Selection and Quality Assessment

All search results were managed using EndNote X20. Duplicate entries were removed, and each article underwent title and abstract screening by the lead reviewer, followed by full-text assessment for eligibility. Quality was evaluated based on transparency of methodology, availability of datasets or code, robustness of validation protocols, and acknowledgement of limitations or biases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework guided documentation of the selection process.[31]

3. Case Studies of AI used to reduce animal testing for new drug discovery:

1. Recursion Pharmaceuticals — InVivoPrint (AI for in-vivo phenotyping and early toxicity detection)

Overview: Recursion built one of the broadest industrial platforms combining high-content cellular imaging, "smart cage" in-vivomics, and deep learning to detect early phenotypic signatures of efficacy and toxicity. Their InVivoPrint V1 model integrates time-series behavioural and physiologic readouts from instrumented animal housing with traditional assay endpoints to flag liabilities earlier in preclinical pipelines.

Methods / AI approach: The company collects continuous video and sensor streams (activity, temperature, respiration), clinical chemistry, haematology, and other metadata across thousands of animals and assays. A multitask discriminative deep-learning model ingests ~19 heterogeneous inputs and produces compound "fingerprints" of known toxicity signatures; new compounds are compared against these fingerprints to predict organ-level liabilities and adverse outcomes earlier than traditional endpoints.

Effect on animal testing: By recognizing toxicity signals earlier, the platform allows teams to deprioritize hazardous candidates before committing to long, large-cohort studies. This "triage upstream" reduces the number and duration of follow-on in-vivo experiments, reduces repeat studies, and focuses animal use on targeted confirmatory work. Public reporting indicates program timelines shortened substantially (Recursion cites examples of moving a candidate to clinical testing in ~18 months versus multi-year industry norms).

Outcomes & evidence: Recursion's published descriptions and press coverage report earlier detection of organ toxicities and faster candidate progression. However, company-level animal-count reductions are program-specific and often proprietary; academic validation is emerging but not yet universal.

Limitations: Models depend on rich, standardised data; generalizability across labs and species requires validation. Regulatory acceptance for complete replacement remains limited — the approach is currently hybrid (computational + reduced targeted in vivo).[32]

2. Insilico Medicine — AI-designed candidates and accelerated preclinical pipelines

Overview: Insilico Medicine has demonstrated rapid target identification, design and nomination of preclinical candidates using generative and reinforcement learning approaches; one high-profile program advanced an anti-fibrotic candidate to Phase I in ~30 months from project start. Their workflows prioritise human-relevant in-silico and in-vitro

predictions that reduce the need for broad exploratory animal screening.[33]

Methods / AI approach: Insilico uses generative chemistry models (GANs/transformers/reinforcement learning), integrated with in-silico ADMET predictors and in-vitro human cell assays, to design and triage molecules before any animal work. Candidate selection emphasizes predicted human biology relevance and safety profiles, decreasing the number of molecules requiring animal toxicology screening.

Effect on animal testing: Faster, higher-confidence candidate selection reduces initial animal screening breadth and the iterative animal cycles common to empirical medicinal chemistry. In reported programs Insilico progressed leads with more focused, confirmatory in-vivo testing rather than broad discovery-era animal screens.

Outcomes & evidence: Public timelines (e.g., Phase I entry within ~30 months) and peer-reviewed publications show accelerated programs. Quantified reductions in animal counts are rarely disclosed publicly but process changes imply meaningful reductions in exploratory animal experiments.

Limitations: As with other AI workflows, translational uncertainty remains: in-silico models simplify biology and can miss emergent in-vivo phenomena; regulatory packages still require targeted in-vivo safety data.[33,34]

3. Exscientia (and DSP-1181) — AI-driven design to shrink discovery timelines and de-risk animal testing

Overview: Exscientia collaborated with Sumitomo Dainippon Pharma to create DSP-1181 (for OCD), one of the first AI-designed small molecules to reach clinical trials. The project illustrated compressed lead optimization cycles and fewer candidate syntheses and screens in early discovery.

Methods / AI approach: Exscientia applies knowledge-driven AI and active learning across target-binding models, multi-parameter optimization (MPOS) and automated synthesis/assay loops. These tools seek to generate molecules that balance potency, selectivity and predicted ADMET properties up front — reducing the need to test many analogue series in animals.[35]

Effect on animal testing: By narrowing candidate sets before preclinical selection, Exscientia's approach lowers the number of compounds entering animal tolerability and pharmacology studies. Their reported discovery timelines (e.g., single-year discovery phases) suggest fewer iterations requiring animal work.

Outcomes & evidence: DSP-1181's progression to Phase I was widely reported as evidence that AI methods can reach clinical-stage candidates faster than typical routes; yet detailed animal-use numbers remain corporate and program-specific.

Limitations: AI design reduces but doesn't eliminate animal testing requirements. Confirmatory pharmacology, safety pharmacokinetics, and regulatory-mandated toxicology studies still use animals. External validation of AI predictions across diverse chemotypes is ongoing.[36]

4. Atomwise — structure-based virtual screening to cut experimental and animal screening burden

Overview: Atomwise's Atom Net and related deep convolutional models perform large-scale virtual screening and de-prioritization of compounds before synthesis and biological assays. Virtual triage reduces the scale of wet-lab high-throughput screening (HTS) and downstream animal pharmacology tests.

Methods / AI approach: Atomwise uses 3D convolutional neural networks trained on protein–ligand complexes to predict binding and prioritise chemical matter. This enables in-silico filtering of millions of compounds and selection of a much smaller, higher-quality set for biochemical and cellular assays.

Effect on animal testing: By reducing false positives and focusing bench testing on likely actives, Atomwise's platform reduces the downstream animal experiments used to triage initial hits in traditional workflows. Fewer false leads entering in vivo pharmacology reduces animal usage and cost.

Outcomes & evidence: Case examples and company reports highlight improved hit rates and fewer compounds needing follow-up in experimental pipelines; independent peer literature corroborates that effective in-silico triage can shrink follow-on animal testing. However, company-wide animal-use numbers are not publicly quantified.

Limitations: Predictive performance depends on accurate structural models and high-quality training data; off-target and ADMET liabilities still require empirical assessment. Virtual hits must be validated in vitro and often in vivo.[37,38]

5. DeepMind / AlphaFold — high-accuracy structure prediction enabling hypothesis-driven work and fewer animal experiments

Overview: AlphaFold (and its successors) transformed access to high-quality protein structures for nearly all known proteins. Structure knowledge accelerates rational ligand design, antigen engineering and mechanistic hypotheses that reduce exploratory animal studies.

Methods / AI approach: AlphaFold predicts 3D protein structures from sequence with high accuracy, enabling computational docking, interaction mapping, and protein engineering without the need for resource-intensive structural biology pipelines. These predictions inform targeted experiments and reduce blind empirical screens that would have required broader animal follow-up.

Effect on animal testing: Improved mechanistic understanding enables better in-vitro model selection, targeted mutational studies and focused candidate design — collectively reducing the scale of exploratory animal studies. For example, structure-guided antigen design can reduce iterative animal immunization or challenge studies by improving first-pass candidates.

Outcomes & evidence: Thousands of studies now cite AlphaFold structures to prioritise experiments. While AlphaFold itself is not a wet-lab replacement, its use shortens cycles and reduces the quantity of empirical screening that would cascade into animal experiments. The Nobel/major press recognition highlights the paradigm shift.

Limitations: Structure prediction doesn't capture dynamics, post-translational modifications, or complex in-cell contexts comprehensively; in vivo validation remains essential for many endpoints.[39]

6. Benevolent AI — knowledge-graph driven hypothesis generation to de-risk in vivo programs

Overview: Benevolent AI uses a large knowledge graph combining literature, chemistry, genomics, clinical data and ontologies to generate mechanistic hypotheses, prioritise targets and select repurposing candidates. Focused, evidence-backed hypotheses reduce exploratory in-vivo studies and accelerate translational choices.[40]

Methods / AI approach: Semantic networks and graph learning identify non-obvious target–disease links and suggest existing molecules with higher translational potential. The platform layers predicted mechanism-of-action evidence and safety signals to deprioritise risky paths early.

Effect on animal testing: By redirecting resources toward candidates with mechanistic plausibility and pre-existing safety data (repurposing), BenevolentAI reduces the amount of first-pass animal pharmacology often needed for novel targets and broad screening campaigns.

Outcomes & evidence: BenevolentAI has produced testable hypotheses and candidate programs adopted by pharma partners; these programs claim faster progression and fewer exploratory animal studies, but granular animal-use metrics are typically proprietary.

Limitations: Knowledge-graph inferences depend on literature completeness and may inherit biases in published data; experimental confirmation (often including targeted animal tests) remains necessary.[41]

7. Deep Genomics — AI for sequence-to-phenotype prediction and reduced animal screening in genetic therapeutics

Overview. Deep Genomics applies deep learning to predict the effects of genetic variants and to design oligonucleotide therapeutics (e.g., splice-modulating antisense oligos). Their platform enables precise, model-informed candidate design and in-vitro prioritisation, reducing broad animal screening for genetic targets.[42]

Methods / AI approach: The company's platform integrates transcriptomic, genomic and biochemical data to predict variant consequences and to design corrective sequences. Predictions guide which constructs are advanced to cellular and animal testing, concentrating resources on the most promising constructs.

Effect on animal testing: By improving the success rate of in-vitro to in-vivo translation, Deep Genomics reduces the number of oligonucleotide variants that must be tested in animals and shortens iterative design cycles that previously drove repeated animal use.

Outcomes & evidence. Company pipelines and partnerships show more targeted preclinical programs with fewer exploratory in vivo experiments. Peer literature supports that accurate in-silico guide design reduces off-target risks and animal attrition.

Limitations: Predictive models require broad, high-quality genomic datasets; organismal context may still reveal unpredicted biology necessitating animal studies. Regulatory safety assessment for oligonucleotides still involves in vivo components in many jurisdictions.[43]

3.1 Historical Evolution:

The integration of computational methods into drug discovery dates back to the 1960s with the introduction of computer-aided drug design (CADD). Quantitative structure–activity relationship (QSAR) models in the 1970s marked the first attempts to correlate molecular features with biological activity using statistical methods. The 1980s and 1990s saw the rise of molecular docking and virtual screening, supported by increasing computational power.[44]

Machine learning gained prominence in the late 1990s, as algorithms like Random Forests and Support Vector Machines began to outperform linear models in QSAR predictions. The 2000s ushered in the deep learning (DL) era, where artificial neural networks could capture complex, non-linear relationships across vast datasets. By the mid-2010s, convolutional neural networks (CNNs) and recurrent neural networks (RNNs) demonstrated unprecedented accuracy in image and sequence analysis, respectively, inspiring their adoption in molecular modelling.

The current wave (2019–2024) is characterised by graph neural networks (GNNs), transformer architectures, and generative models.[45] These methods excel at representing molecular graphs, capturing contextual dependencies, and generating novel structures. Together, they constitute the backbone of AI's transformative impact on pharmaceutical research.[46]

Table 2: Evolution of models in drug discovery- from traditional approaches to AI substitutes:

Sr. no.	Stages of Drug Discovery	Traditional/ pre-AI models	AI- ML Substitutes	Advantages of AI Models
1.	Target Identification	Literature-based manual curation experimental genomics screens- QSAR linear regression models	Natural language processing for text mining- omics integration using Deep learning- graph neural network (GNNs) for protein- protein networks.	Faster identification novel targets; integrating multi-omics and tell data; detects hidden biological patterns
2.	Hit Discovery and Screening	High-throughput screening with millions of composures molecular docking with static scoring function	AI- enhanced HTS using CNN/RNN- virtual screening with GNNs and transformers- DiffDock.	Higher accuracy, reduces false possible explores larger chemical space; captures binding uncertainly.
3.	Lead Optimization	Medicinal chemistry intuition- rule-based QSAR refinement- SAR by manual iteration.	Reinforcement learning (RL) for de-novo design- generative adversarial networks (GANs) for molecular creation- multi-objective optimization with ML	Produces novel scaffolds, balances potency, selectivity ADMET simultaneously.
4.	ADME and Toxicology predication	In-vitro cell-based assays- in-vivo animal studies- rule-based QSAR toxicity prediction	Transformer embeddings (ChemBERTa, ProBert for ADMET- GNNs for Physiological based pharmacokinetics (PBPK)- ensemble ML models for toxicity	Early, cost effective prediction; reduces animal use; higher accuracy with larger datasets.
5.	Clinical Trail designs	Manual protocol design- Broad inclusion criteria- Traditional statistical models	AI- driven patient stratification (trail pathfinder)- ML based dose optimization predictive models for dropout/ enrolment	Faster recruitment smaller sample size, more personalized designs, improved statistical power
6.	Drug Repurposing	Serendipitous discovery- manual literature mining off-label clinical observation	Meta- learning frameworks (meta-GAT)- LLM- based frameworks (DrugReAlign) Knowledge graph mining	Systematic exploration of old drugs; reduce cost, time identified hidden therapeutic opportunities. [47]

3.2 Core Paradigms

1. Classical Machine Learning: Encompasses decision trees, Random Forests, Support Vector Machines, and k-nearest neighbors, which continue to play a significant role in drug discovery and predictive modeling. These algorithms are particularly advantageous when working with limited datasets, where the complexity of deep learning models may not be justified. Their ability to provide clear decision boundaries and interpretable outputs makes them valuable in regulatory settings and hypothesis generation. Moreover, classical methods often require lower computational resources, making them accessible for resource-limited research environments, while still delivering robust performance across classification, regression, and clustering tasks.[48]

2. **Deep Learning:** Utilises multilayer neural networks capable of extracting hierarchical features from complex, high-dimensional datasets, enabling superior performance compared to classical approaches. This paradigm has shown remarkable success in quantitative structure–activity relationship (QSAR) modeling, where it captures subtle molecular descriptors beyond human interpretation. Deep learning is also transformative in image-based screening, allowing automated recognition of phenotypic changes in cells or tissues. Additionally, it plays a critical role in predicting ADMET properties by integrating genomics, chemical features, and pharmacokinetic data. While requiring large datasets and computational power, its predictive accuracy and scalability make it indispensable for modern drug discovery pipelines.[49]

3. Graph Neural Networks (GNNs): Represent molecules as graphs where atoms are treated as nodes and bonds as edges, allowing direct learning from molecular structures without handcrafted features. By propagating and aggregating information through these graph representations, GNNs can capture both local chemical environments and global relational properties.

Variants such as Graph Convolutional Networks (GCNs) emphasise neighbourhood feature aggregation, while Graph Attention Networks (GATs) introduce attention mechanisms to weigh important atomic interactions. These models have achieved state-of-the-art results in molecular property prediction, toxicity assessment, and drug–target interaction studies, making them powerful tools for structure-based drug discovery and design.[50]

4. Transformer Models: Originally designed for natural language processing, transformers utilise self-attention mechanisms to capture long-range dependencies and contextual relationships within sequences. When adapted to molecular science, compounds are treated analogously to sentences, with atoms or substructures serving as tokens. Models like Mol-BERT and ChemBERTa generate rich contextual embeddings of chemical structures, enabling precise prediction of molecular properties, bioactivity, and drug–target interactions. Unlike traditional descriptors, these embeddings are learned directly from large-scale chemical databases, improving generalizability across tasks. Transformers thus provide a scalable and data-driven framework for molecular representation learning, establishing themselves as powerful tools in modern AI-driven drug discovery.

5. Reinforcement Learning (RL): A branch of machine learning designed for sequential decision-making; RL has emerged as a powerful paradigm in generative molecular design and optimisation processes. In RL, an agent interacts with an environment by taking actions and receiving feedback in the form of rewards, gradually learning strategies that maximise long-term objectives. Applied to drug discovery, RL facilitates the generation of novel molecules by optimising for multiple properties simultaneously, such as potency, selectivity, solubility, and toxicity. Unlike static predictive models, RL enables iterative refinement, mimicking the decision-making process of a medicinal chemist but at scale. Importantly, RL can balance *multi-objective optimisation, a frequent challenge in drug design, where* improving one property often compromises another. Coupled with deep learning architectures and molecular representations like graphs or SMILES strings, RL has demonstrated success in de novo drug design, scaffold hopping, and lead optimisation, significantly accelerating discovery while reducing reliance on costly trial-and-error experimentation.[51]

6. Large Language Models (LLMs): Large Language Models, originally developed for natural language processing, are now being adapted to biomedical and chemical sciences, offering transformative opportunities in drug discovery. By training on massive text corpora that include chemical literature, patents, clinical trial data, and curated knowledge bases, LLMs acquire contextual understanding of biomedical terminology, molecular structures (via SMILES or InChI strings), and disease associations. This enables applications ranging from automated literature mining and extraction of drug–target relationships, to hypothesis generation for novel therapeutic strategies. Importantly, LLMs can facilitate drug repurposing by uncovering hidden associations between existing compounds and new disease indications.[52] With few-shot and zero-shot learning capabilities, these models can generalise to new tasks with minimal additional training, accelerating knowledge discovery. Moreover, when integrated with structured chemical and biological datasets, LLMs provide interdisciplinary insights, bridging clinical, genomic, and chemical information—thereby becoming invaluable tools for knowledge-driven, human-centric innovation in pharmaceutical research.[53]

3.3 Ethical and Regulatory Considerations:

Table 3: Ethical and Regulatory Considerations in AI-driven Drug Discovery

Dimension	Challenge	Implication for Drug Discovery	Regulatory/Ethical Focus
Data Bias	Overrepresentation of certain populations or diseases in training datasets	Skewed predictions, poor generalizability, inequities in healthcare outcomes	Promote diverse, representative datasets; fairness audits
Interpretability	Complexity of deep models (black-box problem)	Regulators and clinicians cannot easily verify predictions	Develop explainable AI, mandate interpretable outputs
Validation Standards	Lack of consensus on model benchmarking and reproducibility	Inconsistent regulatory acceptance, risk of unsafe decisions	FDA, EMA working on AI validation guidelines
Transparency	Limited insight into algorithm decision-making processes	Erodes trust among stakeholders, complicates adoption	Documentation, algorithm disclosure, transparent reporting
Accountability	Ambiguity in assigning responsibility for AI-generated errors	Potential medicolegal disputes, ethical risks	Clear liability frameworks and developer accountability

Fairness and Equity	Bias against minority or underserved groups	Risk of exacerbating disparities in clinical trials and drug access	Design equity-focused protocols, diverse clinical datasets
Privacy and Security	Use of sensitive patient data in training models	Data misuse or leakage undermines patient trust	Compliance with GDPR, HIPAA, robust encryption
Ethical Principles	Balancing rapid innovation with patient safety	AI-driven drug decisions could prioritise speed over welfare	Uphold 3Rs, transparency, patient-centric approaches [56]

4. Applications Across the Drug Discovery Pipeline

4.1 Target Identification:

4.1.1 Natural Language Processing (NLP)

Natural Language Processing (NLP) plays a pivotal role in drug discovery by systematically mining the immense volume of biomedical literature, which contains valuable yet often untapped knowledge. Through tasks like named entity recognition (NER) and relationship extraction, NLP tools can identify connections among diseases, proteins, pathways, and compounds from millions of research articles and abstracts [57]. This capability accelerates hypothesis generation, helping researchers uncover novel targets, biomarkers, or repurposing opportunities that could otherwise remain hidden. In recent years, transformer-based architectures such as BioBERT and SciBERT have significantly improved the accuracy of biomedical text understanding, outperforming earlier statistical or rule-based methods. These models leverage contextual embeddings to capture subtle semantic relationships, advancing automated literature mining. However, limitations remain. NLP models can inherit biases from their training corpora, leading to skewed outputs, and they often lack sufficient integration of real-world clinical data to contextualize findings for translational research, necessitating further refinement and validation.[58]

4.1.2 Omics Data Integration

The rapid expansion of high-throughput technologies has generated vast amounts of data across genomics, transcriptomics, proteomics, metabolomics, and epigenomics. Analysing this high-dimensional and heterogeneous information requires advanced AI techniques capable of uncovering meaningful biological insights. Supervised learning methods are widely employed for biomarker identification, enabling precise prediction of disease states, drug responses, and patient stratification. Meanwhile, unsupervised approaches such as clustering reveal hidden disease subtypes and molecular signatures that may inform personalised therapeutic strategies. Importantly, cross-validation against established biological pathways and curated knowledge bases enhances both interpretability and confidence in AI-derived findings. These integrative approaches facilitate a systems-level understanding of disease mechanisms, ultimately improving target discovery and translational outcomes. Despite these advantages, significant challenges remain. Variability in sample preparation, sequencing platforms, and data processing pipelines across laboratories introduces inconsistency. The lack of standardised protocols impedes reproducibility and comparability, underscoring the urgent need for harmonised guidelines in omics-driven AI research.[59]

4.1.3 Molecular Similarity Analysis

Molecular similarity analysis leverages chemical fingerprints and descriptors to detect compounds structurally related to known bioactive molecules. AI models enhance this process by enabling rapid screening and prioritisation of candidates, often guiding lead identification. Advanced approaches like Graph Neural Networks (GNNs) capture complex, non-linear relationships between molecular substructures, improving accuracy. However, these methods remain limited by the breadth and diversity of existing chemical databases such as ChEMBL and ZINC.[60]

4.1.4 Network Pharmacology

AI-enhanced network pharmacology integrates protein–protein interaction maps, pathway databases, and omics data into graph models. GNNs facilitate identification of key regulatory nodes. This systemic approach highlights multitarget strategies for complex diseases but risks bias if underrepresented pathways are excluded from datasets.[61]

4.2 Lead Discovery and Optimization:

4.2.1 AI-Enhanced High-Throughput Screening

High-throughput screening (HTS) enables rapid testing of large chemical libraries but is often costly, time-consuming, and prone to false positives. AI enhances this process by prioritising compounds with predicted activity before experimental validation, thereby reducing the volume of unnecessary assays. Through approaches such as transfer learning, models trained on multi-fidelity HTS datasets can integrate noisy, large-scale primary screening data with smaller, higher-quality confirmatory assays. This fusion improves predictive accuracy, enabling more efficient selection of promising hits. By guiding experimental efforts, AI-driven HTS accelerates early-stage discovery, lowers costs, and enhances reliability compared to conventional, purely empirical pipelines.[62]

4.2.2 Virtual Screening and Structure-Based Design

Virtual screening and structure-based design have been revolutionised by AI, particularly deep learning, which enables accurate prediction of ligand–target binding affinities and efficient filtering of vast compound libraries. Graph Neural Networks (GNNs) and transformer architectures capture intricate molecular

interactions, including atom-level dependencies and spatial features critical for drug–target recognition. Beyond predictive tasks, generative models like DiffDock apply diffusion-based approaches to forecast ligand binding poses, incorporating conformational flexibility and uncertainty estimates. This holistic representation allows better identification of stable binding modes, improving hit rates in virtual screening. By integrating accuracy with scalability, AI-driven methods streamline lead discovery and optimisation.

Virtual screening and structure-based design are increasingly empowered by AI, offering a faster and more precise route to identifying promising drug candidates. Deep learning models can estimate drug–target binding affinities, effectively narrowing down vast chemical libraries to compounds with higher therapeutic potential. Graph Neural Networks (GNNs) and transformer models capture complex structural and relational features, enabling accurate representation of molecular interactions beyond traditional docking techniques. Additionally, generative approaches such as DiffDock leverage diffusion models to predict ligand binding poses, explicitly considering molecular flexibility and structural uncertainty. This combination of predictive power and generative modelling enhances screening efficiency, improving success rates in lead identification and rational drug design.[63]

4.2.4 Drug Repurposing

Drug repurposing leverages existing compounds for new therapeutic indications, and AI has greatly expanded this field by integrating and analysing diverse biomedical datasets. Advanced methods such as meta-learning frameworks and large language model (LLM)-based systems like DrugReAlign enable knowledge transfer across domains, predicting novel repurposing opportunities with higher accuracy. The key advantages include substantially reduced development costs, shorter timelines, and the benefit of established safety profiles from prior use. However, significant challenges persist, particularly in validating AI-generated predictions across heterogeneous patient populations, where genetic, demographic, and clinical variability may influence drug response, necessitating rigorous experimental and clinical validation.[64]

4.3 ADMET, Toxicology, and Clinical Development:

4.3.1 Predictive Toxicology

Predictive toxicology has become one of the most impactful areas where AI contributes to reducing reliance on traditional animal testing. By leveraging chemical structure descriptors, bioassay data, and multi-omics inputs, AI models can forecast a wide range of toxicity endpoints including mutagenicity, cardiotoxicity, hepatotoxicity, nephrotoxicity, and immunotoxicity. Emerging transformer-based embeddings, such as ChemBERTa for molecular data and ProBert for protein-related features, capture richer contextual and structural information than conventional fingerprints or rule-based toxicophores. These models facilitate more accurate predictions of off-target effects, dose-dependent toxicities, and organ-specific liabilities at earlier stages of the pipeline. Moreover, integration of natural language processing with toxicology databases enables knowledge mining from vast literature and safety reports, improving signal detection for rare adverse events. Despite these advancements, reproducibility and cross-species generalisation remain challenging, emphasising the need for robust benchmarks, curated datasets, and regulatory frameworks to establish AI-driven toxicology as a reliable alternative to animal-based safety testing.[65]

4.3.2 Pharmacokinetic Modelling

Pharmacokinetic (PK) modelling is essential for understanding how drugs are absorbed, distributed, metabolised, and excreted in the human body. Traditional physiologically based pharmacokinetic (PBPK) models rely heavily on parameter estimation from animal studies, which often introduces translational inaccuracies. The integration of AI, particularly Graph Neural Networks (GNNs), has advanced PBPK approaches by simulating tissue-specific drug distribution based on chemical structure, molecular interactions, and physiological context. GNNs can capture the nonlinear relationships governing drug transport across biological compartments, providing more reliable predictions of critical PK parameters such as clearance, half-life, and volume of distribution. Additionally, deep learning models enhance the prediction of enzyme–substrate interactions and transporter effects, further refining drug metabolism forecasts. By integrating real-world clinical and omics data, AI-enhanced PBPK models promise to significantly reduce dependence on animal-derived inputs, while offering personalised simulations tailored to patient demographics, genetics, or comorbidities—supporting safer and more effective dose optimisation in precision medicine.[66]

4.3.3 Clinical Trial Optimisation

Artificial intelligence is increasingly shaping the design and execution of clinical trials, addressing inefficiencies that often delay drug development. By analysing electronic health records, genomic data, and patient demographics, AI helps refine inclusion and exclusion criteria, ensuring that trials enrol more representative cohorts. Predictive models estimate dropout risks and adherence patterns, allowing proactive mitigation strategies. Tools like Trial Pathfinder have shown that AI-based simulations can reduce trial sample sizes while maintaining statistical power, improving cost-effectiveness. In oncology, AI-driven patient–trial matching has accelerated recruitment by aligning molecular profiles with trial eligibility, ultimately enhancing trial outcomes and supporting patient-centric research.[67]

5. Comparative Analysis of AI Methodologies:

Classical ML methods (Random Forests, SVMs) remain competitive in small datasets and provide transparency. GNNs excel at modelling molecular graphs, capturing structural complexity. Transformers, with their attention mechanisms, achieve state-of-the-art results in sequence- and context-based tasks.

However, complexity does not always guarantee superior performance. In some ADMET tasks, simpler algorithms match or exceed deep models when hyperparameters are optimised. Interpretability remains a strength of classical methods, whereas modern architectures are often criticised as opaque. A hybrid approach that combines interpretability with predictive power may be the optimal path forward.[68]

6. Challenges, Limitations, and Controversies:

1. Data Quality and Accessibility: AI models are only as strong as their training data. Public datasets often reflect demographic or experimental biases, limiting generalizability. Initiatives like LIT-PCBA and MF-PCBA aim to provide unbiased, standardised benchmarks.

2. Interpretability and the "Black Box" Problem: Complex architectures hinder understanding of model outputs, complicating regulatory approval and scientific trust. Explainable AI techniques are urgently needed.

3. Ethical Concerns: Data ownership, algorithmic bias, and unequal access to computational infrastructure risk exacerbating health inequities.

4. Regulatory Hurdles: Agencies are still developing frameworks for validation of AI models in drug development, slowing adoption in clinical practice.

5. Skill Gap: Successful implementation requires interdisciplinary expertise in AI, chemistry, and pharmacology. Workforce training remains a bottleneck.

7. Estimated Reduction in Animal Testing:

1. AI Impact in Neurology and Drug Discovery:

Up to 70% fewer animal experiments are required in early drug development—especially in neurology—when AI predicts efficacy and toxicity in silico.

For example, prediction models can replace a significant portion of animal tests, leading to major time and cost savings.

2. AI Bio Simulation Platforms:

Platforms like VeriSIM Life's BIOiSIM have helped reduce animal testing by more than 50% in practical drug development scenarios.

The company also reports that Roche has reduced its use of animals in experimental testing by almost 40% over the past eight years, thanks in part to AI and simulation tools.

3. Regulatory and Broader Trends:

FDA and NAM (New Approach Methodologies): The FDA is actively encouraging a shift away from animal testing, promoting AI, organ-on-a-chip, and human cell–based models. These methods are broadly intended to reduce and potentially replace animal testing in regulatory pathways.

Historical Trend in Animal Use: In a broader context (not AI-specific), animal use in drug-related research has fallen—from about 30% of all animal use in 2005 to approximately 20% today (in Europe). This reflects broader methodological shifts and ethical pressures.[69]

7. Future Directions and Research Gaps:

1. Explainable AI (XAI): Essential for regulatory acceptance and clinical trust.

2. Multimodal Integration: Combining chemical, biological, imaging, and clinical data to create holistic models.

3. Federated Learning: Enables training across institutions without sharing raw data, preserving privacy while enhancing dataset diversity.

4. Generative AI: Continued development of diffusion models, GANs, and reinforcement learning for de novo design.

5. Democratisation of Tools: Open-source platforms and cloud-based services are needed to ensure equitable access.

6. Clinical Translation: More emphasis on prospective clinical validation rather than retrospective benchmarking.[70]

8. Conclusion:

Artificial intelligence is emerging as a transformative force in drug discovery, offering innovative, data-driven solutions to address the fundamental challenges of high costs, extended development timelines, and low clinical success rates that have long hindered the pharmaceutical pipeline. By harnessing advanced architectures such as graph neural networks, transformer models, reinforcement learning frameworks, and large language models, AI has demonstrated a measurable impact across the entire spectrum of drug discovery—from target identification and lead optimisation to toxicity prediction and clinical trial design. Importantly, these innovations align closely with ethical imperatives by reducing reliance on traditional animal studies, thereby advancing the principles of Replacement, Reduction, and Refinement (3Rs).

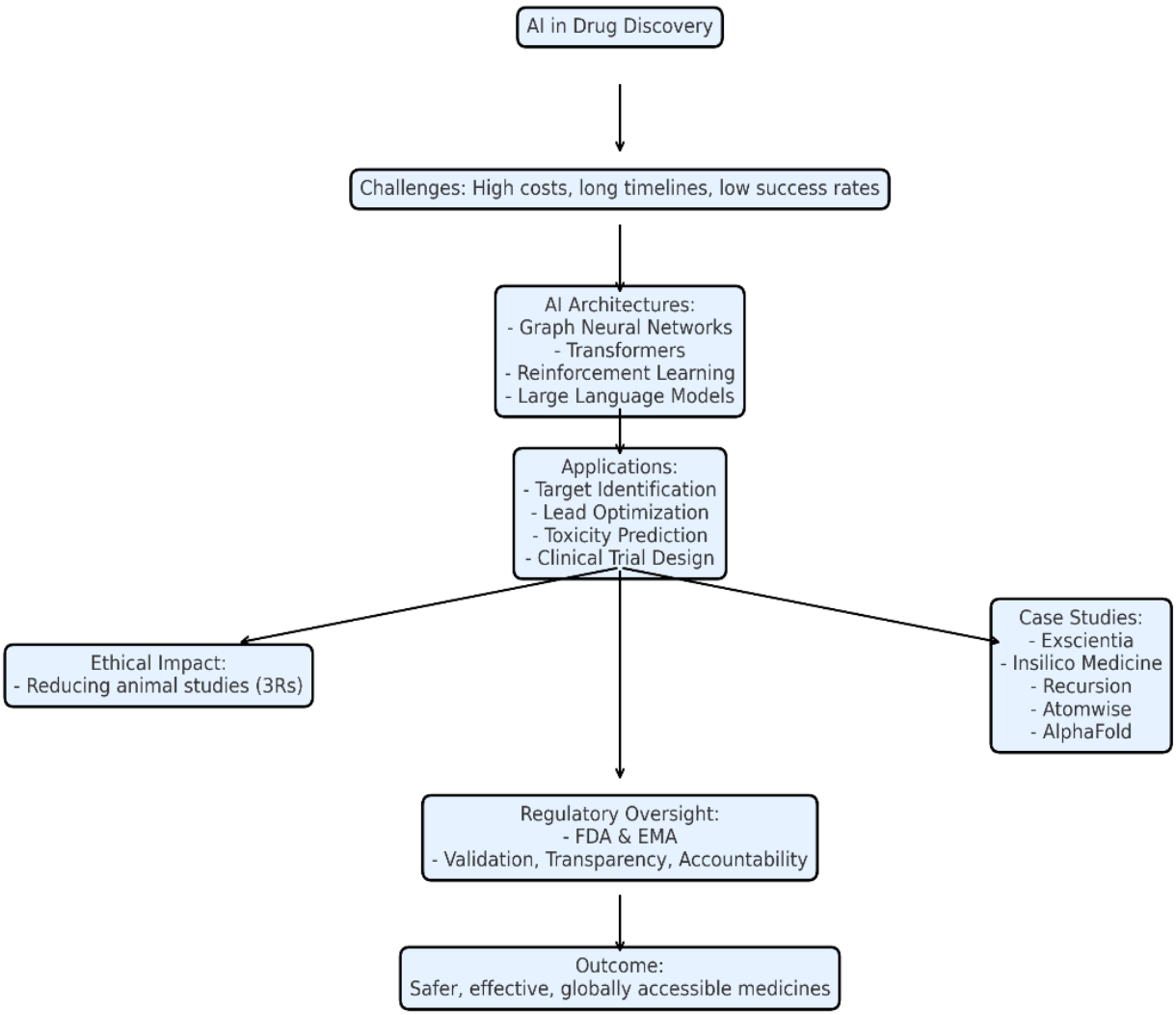

Figure 2: AI in Drug Discovery Conclusion Flowchart

The case studies presented, including platforms from Exscientia, Insilico Medicine, Recursion, Atomwise, and AlphaFold, highlight how AI has already shortened discovery timelines, improved predictive accuracy, and streamlined decision-making. Applications in predictive toxicology, pharmacokinetic modelling, and trial optimisation further illustrate AI's capacity to minimise unnecessary in vivo experimentation while enhancing translational efficiency. At the same time, regulatory bodies such as the FDA and EMA continue to explore frameworks for validation, transparency, and accountability, underscoring the need for explainable and equitable AI systems.

AI-driven drug discovery should not be viewed merely as a computational tool but as a paradigm shift that requires cultural, regulatory, and ethical adaptation. If responsibly integrated, AI can enable the development of safer, more effective, and globally accessible medicines, ultimately redefining the future of healthcare.

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