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Review

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Ophthalmic drug discovery and development using artificial intelligence and digital health technologies

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Globally, drug discovery and development programs are complex, multi-decade long and prohibitively expensive. Artificial intelligence (AI) and other digital health technologies have the potential to enhance and accelerate each stage of drug discovery and development, from pre-clinical target identification to post-market repurposing, and even revolutionize the entire process. Using ophthalmology as an example, this review highlights recent AI and digital health innovations in different phases of drug discovery and development. By leveraging machine learning algorithms and vast clinical and multiomics datasets, AI can rapidly identify and validate new drug targets, optimize lead compounds, and predict pharmacokinetics, pharmacodynamics and toxicity. AI-assisted multi-modal ocular biomarkers may improve treatment monitoring and support personalized medicine. Integrating AI shortens development timelines, enhances efficiency, reduces costs, and increases the success rate of new drugs. Currently, standardized regulations for AI in ocular drug development are still lacking and urgently needed to ensure safe and equitable implementation.

Drug discovery and development programs are complex, involving public-private partnerships, and typically are multi-decade long, and hugely expensive (Fig. 1). The cost of developing a new drug is estimated between 314 million and $4.4 billion[1]. Using ophthalmology as an example, the global ophthalmic drug market is expected to reach $66 billion by 2030, with significant investments in major sight-threatening conditions like age-related macular degeneration (AMD) and diabetic retinopathy[2]. Bevacizumab, originally developed for cancer, look over 20 years and billions of dollars before being "discovered" accidentally and repurposed for treatment of AMD[3,4]. This led to the progressive discovery and development of anti-vascular endothelial growth factor (VEGF) therapy specific for eye diseases, including AMD, diabetic retinopathy and retinal vein occlusions, which has led to considerable decline in blindness in many countries[5–9]. However, the process from identifying the VEGF target to obtaining US Food and Drug Administration (FDA) approval for the use of anti-VEGF agents in the eye took more than 30 years (Fig. 2). Since 2010, only 17 new drugs have gained regulatory approval from FDA for eye diseases, focusing on conditions such as AMD, open angle glaucoma, and dry eye disease (Table 1). Thus, there remains a pressing need for faster and more innovative treatment strategies for many blinding eye conditions. For instance, no current approved treatment improves visual acuity or reverses geographic atrophy (GA) in late dry AMD patients. Gene therapy (e.g., Luxturna), improves night vision but is only effective for patients with RPE65 gene mutations[10]. The recent UK Clinical Eye Research Strategy study (published in 2024) identified 12 main research themes, including cataract prevention, microbial keratitis treatment, community optometric care pathways, deterring refractive error progression, early detection of childhood visual disorders, and treatment of glaucoma, neurodegeneration, dry AMD, and orbital inflammatory diseases[11].

Artificial intelligence (AI) has emerged as a promising tool to enhance and accelerate the drug discovery process. AI encompasses a range of machine learning (ML) and deep learning (DL) techniques capable of analyzing vast datasets, identifying complex patterns, and generating predictive models. These capabilities are particularly valuable in drug discovery,

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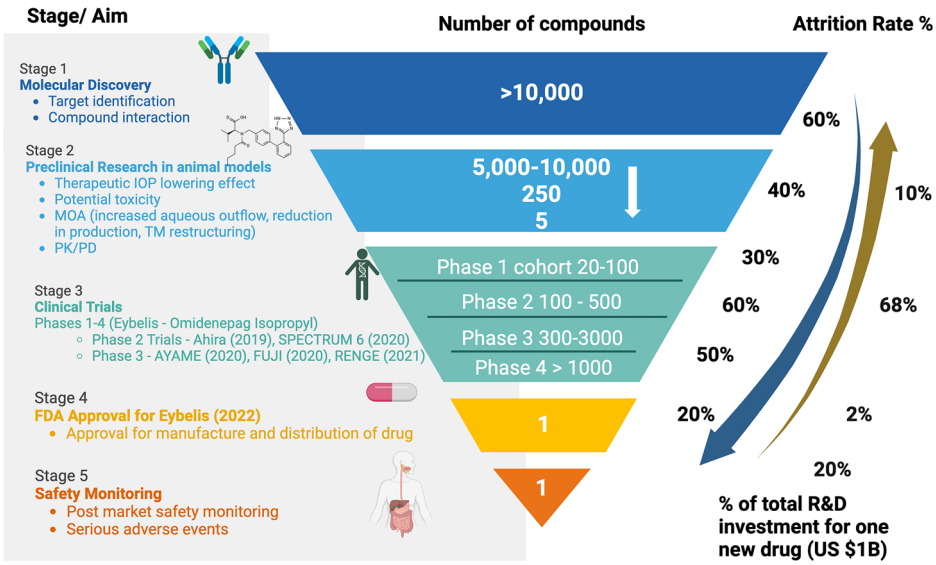

Fig. 1 | Phases, attrition rate, and investment in ophthalmic drug discovery and development. This figure outlines the key stages, attrition rates, and financial investment required in the drug discovery and development process, using ophthalmology as an example. The process begins with target identification and compound screening, followed by preclinical studies assessing efficacy, toxicity, and PK/PD using in silico, in vitro, and in vivo models. Clinical development progresses through Phases I to IV, involving increasing cohort sizes to evaluate safety, dosage, efficacy, and long-term outcomes. Each stage faces significant attrition, with fewer than 1 in 10,000 compounds reaching approval. The average cost per successful drug has been estimated at $172.7 million (2000–2018). Post-market surveillance continues to assess safety and adverse events after regulatory approval. An ophthalmic case study of omidenepag isopropyl (Eybelis), a topical treatment for IOP reduction in glaucoma and ocular hypertension, exemplifies this pipeline. This structured process ensures that only the most promising and safe treatments reach patients. PK/PD pharmacokinetics/pharmacodynamics, FDA Food and Drug Administration, IOP intraocular pressure. Figure created with BioRender.com.

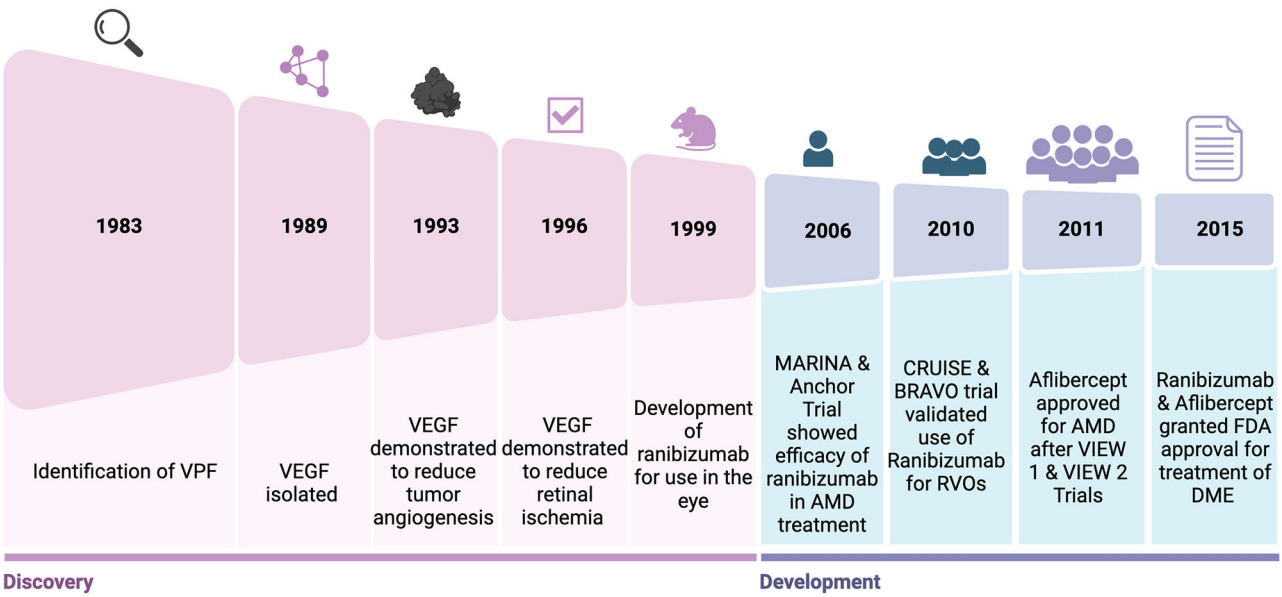

Fig. 2 | Timeline of anti-VEGF drug discovery and development. This figure presents the key milestones in the discovery and development of anti-VEGF therapies. Beginning with the identification of VEGF as a vascular permeability factor in 1983, the timeline traces VEGF isolation, its role in tumor angiogenesis and retinal ischemia, and the development of ranibizumab as a targeted anti-VEGF agent. Clinical trial milestones include the MARINA and ANCHOR studies in 2006 for AMD, followed by the CRUISE and BRAVO trials for RVO in 2010. FDA approval of aflibercept and ranibizumab for AMD and DME marked significant regulatory and therapeutic achievements. VPF vascular permeability factor, VEGF vascular endothelial growth factor, AMD age-related macular degeneration, RVO retinal vein occlusions, DME diabetic macular edema, FDA Food and Drug Administration. Figure created with BioRender.com.

where AI models can optimize molecular design, predict pharmacokinetic properties, and streamline clinical trial processes. Recent advances in AI-driven drug discovery have demonstrated its ability to significantly accelerate drug development timelines (Table 2). For instance, DSP-1181, an AI-designed drug for obsessive-compulsive disorder, was developed by Sumitomo Dainippon Pharma in collaboration with Exscientia in just 12 months—far shorter than the industry average of 5 years[12]. Exscientia's AI platform optimized the drug's chemical structure, pharmacological activity, and toxicity profile, highlighting AI's potential to expedite early-stage drug development. Halicin, developed by an AI model at MIT, is structurally distinct from conventional antibiotics and effective against drug-resistant bacteria[13]. By screening over 100 million molecules, AI identified novel antibacterial compounds much faster than the traditional experimental screening method[14]. Recent studies show that AI integration can cut early-stage development time by over 60% and increase the likelihood of clinical success, particularly in protein-based drugs, by improving the accuracy of efficacy, safety, and manufacturability predictions[15]. In addition, large language models (LLMs) and vision-language models (VLMs) have introduced a new level of capability, enabling AI to generate novel molecular structures, predict drug-target interactions, and analyze vast biomedical literature at an

Table 1 | Summary of FDA's Center for Drug Evaluation and Research (CDER) approved novel drugs for eye diseases between 2010 and 2024

Drug compound	Brand name	Mechanism of action	Disease	FDA approval	EMA approval
Perfluorohexyloctane	Miebo	Semifluorinated alkane	Dry Eye Disease	2023	NA
Lotilaner	Xdemvy	Ectoparasiticide	Demodex blepharitis	2023	NA
Avacincaptad pegol	Izervay	C5-targeted aptamer	GA secondary to AMD	2023	NA
Tebentafusp	Kimmtrak	gp100 peptide–HLA × CD3 bispecific T-cell engager	Uveal melanoma	2022	2022
Faricimab	Vabysmo	VEGF × ANG2 bispecific antibody	nAMD and DME	2022	2022
Omidenepag isopropyl	Omlonti	Prostaglandin E2 receptor agonist	OAG or OHT	2022	NA
Satralizumab	Enspryng	IL-6R-directed mAb	NMOSD	2020	2021
Teprotumumab	Tepezza	IGF1R-directed mAb	Thyroid eye disease	2020	NA
Brolucizumab	Beovu	VEGF inhibitor	nAMD	2019	2020
Cenegermin	Oxervate	Recombinant NGF	Neurotrophic keratitis	2018	2017
Latanoprostene bunod	Vyzulta	Prostaglandin analog	Intraocular pressure	2017	NA
Netarsudil	Rhopressa/	RHO kinase inhibitor	OAG or OHT	2017	2019 (Rhopressa)
Lifitegrast	Xiidra	LFA1 antagonist	Dry eye disease	2016	NA
Tafluprost	Zioptan	Selective prostaglandin F prostanoid receptor agonist	OAG or OHT	2012	2008 (Taflotan)
Ocriplasmin	Jetrea	Recombinant truncated form of human P plasmin	Symptomatic vitreomacular adhesion	2012	2013
Aflibercept	Eylea	Fusion protein that binds VEGFA and PIGF	nAMD	2011	2012
Alcaftadine	Lastacaft	H1 histamine receptor antagonist	Allergic conjunctivitis	2010	NA

Biosimilars are not included in this table. NA means this drug has not been approved by EMA.
C5 complement 5, *HLA* human leukocyte antigen, *VEGF* vascular endothelial growth factor; *Ang2* Angiopoietin 2, *IL-6R* interlukein-6-receptor, *mAb* monoclonal antibody, *IGF1R* insulin-like growth factor 1 receptor, *LFA* lymphocyte function-associated antigen 1, *PIGF* placental growth factor, *GA* geographic atrophy, *AMD* age-related macular degeneration, *nAMD* neovascular age-related macular degeneration, *DME* diabetic macular edema, *OAG* open-angle glaucoma, *NMOSD* neuromyelitis optica spectrum disorder, *FDA* Food and Drug Administration, *EMA* European Medicines Agency.

unprecedented scale[16]. These models not only enhance scientific research but also improve decision-making in early-stage drug development, clinical trial design, and biomarker identification[17,18].

While several reviews have examined the role of AI in drug discovery, they often focus on individual aspects, such as molecular discovery or clinical trial optimization, without providing a comprehensive perspective[19–22]. Given the rapid advancement in AI and its expanding role across multiple stages of drug development, a broader synthesis is needed. In this review, we aimed to highlight how recent AI advances can facilitate/enable drug discovery and development, starting from pre-clinical target identification to clinical trials and post-trial market repurposing, using ophthalmology as a case study. Compared to general drug development, ophthalmic drug development faces unique challenges as well as opportunities such as its unique route of administration, complex physiological barriers, and potential for imaging biomarkers in characterizing and predicting responses. By addressing these challenges, AI-driven approaches have the potential to accelerate the development of novel ophthalmic therapies, improve patient outcomes, and redefine the future of precision medicine in eye care.

Discovery phase

Target identification

Many eye diseases are associated with protein misfolding and dysregulation, like AMD, cataract, corneal dystrophies, and glaucoma[23]. Understanding their 3D structures is crucial for researchers to comprehend their functions, mechanisms, and roles in diseases. Many drugs work by targeting specific proteins; therefore, identifying the structure of these target proteins can reveal potential binding sites, which is a critical first step in drug design. Traditionally, the gold standards for visualizing protein structures have been X-ray crystallography and/or nuclear magnetic resolution spectroscopy, and now cryo-electron microscopy[24]. However, these methods are extremely costly and time-consuming, and only a very small proportion of the protein structure have been discovered so far with this method[25]. AI-driven approaches have transformed this process by making structural predictions more efficient, and these developments align closely with Computer-Aided Drug Design (CADD), which leverages computational tools to streamline drug discovery[22].

Among all AI-based algorithms developed so far, the AlphaFold series by DeepMind represents a significant breakthrough[26–28]. AlphaFold uses an advanced CNN to predict the 3D structures of proteins based on their amino acid sequences[26]. Over the past few years, AlphaFold has undergone several rounds of refinement, with each version becoming increasingly accurate, including transitioning to a transformer-based block for prediction in AlphaFold2[27]. This advancement has profound implications for drug discovery, particularly in the field of ophthalmology. The ability to accurately predict structure and identify binding site accelerates the drug discovery process, reducing the time and cost of bringing new therapies to market. One group of Chinese researchers used AlphaFold to create 315 abnormal structural isoforms in uveal melanoma patients, providing novel insight into potential targets of treatment[29]. This AI-driven approach reduces the time and cost associated with experimental methods, advancing the field of CADD by incorporating protein structural data into early-stage drug design. The release of AlphaFold3 represents another leap forward in CADD, extending the prediction capabilities from protein structures to DNA, RNA, and their interactions with small molecules[28]. This advancement opens new avenues for nucleic acid-based therapies in ophthalmology, where understanding complex molecular interactions is critical for treating conditions such as retinal degeneration or inherited genetic disorders. AlphaFold3's ability to predict molecular interactions enhances ligand-based design, another core aspect of CADD, by providing detailed structural information on potential drug binding sites.

In addition, AI-driven multi-omics analysis has emerged as another powerful strategy for therapeutic target identification. PandaOmics, an AI-

Table 2 | Summary of drugs in development that utilized AI

Drug compound	Company	Mechanism of action	Disease	Role of AI in drug discovery
DSP 1181[12]	Exscientia & Sumitomo Dainippon Pharma	Serotonin 5 HT1A receptor agonist	Obsessive compulsive disorder	De novo molecular design
AI designed antibody against TL1A[140]	Absci	TL1A targeted antibody	Inflammatory bowel disease	De novo molecular design
ISM3091[141]	Insilico Medicine & Exelixis	IND ready small molecule inhibitor of anticancer target	Cancer	Target Identification & De novo molecular design
Small molecule KAT6A inhibitor[142]	Insilico Medicine & Stemline therapeutics	Small molecule inhibitor for anticancer target	Cancer	De novo molecular design
INS018_055[143]	Insilico Medicine	Small-molecule inhibitor of antifibrotic target TRAF2- and NCK-interacting kinase (TNIK)	Idiopathic pulmonary fibrosis	Target Identification & De novo molecular design
Halicin[144]	MIT	Antibiotic against E coli and Acinetobacter Baumannii	Antibiotic	Drug Repurposing
LP-300[145]	Lantern	Interacts with tyrosine kinase inhibitor (TKI) receptors via cysteine modification.	Relapsed advanced lung cancer	Patient Stratification
LP 184[146]	Lantern	Activated via Prostaglandin Reductase 1 (PTGR1) to its cytotoxic form in cancer cells	Triple negative breast cancer	Lead Optimization and Patient Stratification
LP 284[147]	Lantern	Damages DNA in cancer cells	Refractory lymphomas	Lead Optimization and Patient Stratification

TL1A tumor necrosis factor-like cytokine 1A.

powered platform, integrates gene expression, proteomics, and text-based knowledge graphs to systematically identify and rank potential drug targets[30]. By analyzing diverse molecular datasets, PandaOmics enhances target discovery beyond traditional protein-structure approaches, prioritizing novel, druggable genes for further investigation. Expanding on this concept, AI has also been leveraged to explore non-traditional biological datasets for drug discovery. For instance, one research group employed a multitask deep learning framework to analyze the proteomes of extinct organisms (the "extinctome"), systematically identifying novel antibiotic peptides with therapeutic potential[31,32] Similar AI-driven methodologies have also been applied to the human microbiome, enabling the discovery of antimicrobial peptides with promising therapeutic applications[33,34]. These innovative AI-based strategies in antibiotic discovery highlight a broader shift toward computationally guided drug development, which could similarly transform ocular drug discovery by identifying peptide-based treatments for ocular infections and addressing antimicrobial resistance, a recognized global health threat[14,35].

Computer-aided drug design

After identifying promising targets, the next crucial step is to simulate drug interactions and optimize potential candidates. Structure-based drug design (SBDD) and ligand-based drug design (LBDD) represent two fundamental approaches in CADD. SBDD leverages the 3D structure of biological targets to identify drug candidates. It employs molecular docking to predict the optimal binding orientation and affinity of small molecules, while molecular dynamics (MD) simulations refine these predictions by modeling protein-ligand interactions over time, accounting for flexibility and conformational changes. LBDD, in contrast, focuses on known active compounds rather than target structures. A key method, quantitative structure-activity relationship (QSAR) modeling, uses statistical and machine learning approaches to predict drug efficacy based on molecular features, guiding candidate selection even when structural data is unavailable.

Molecular docking facilitates the examination of the interaction between small molecules and their target proteins. AI-powered docking approaches have revolutionized this process by predicting the binding affinity and orientation of millions of potential drug molecules more quickly and efficiently than traditional methods, as it uses DL models to predict docking outcomes for large chemical libraries[36,37]. For example, Deep Docking can quickly filter and prioritize molecules that may effectively bind to vascular endothelial growth factor (VEGF), a key target in AMD, accelerating the drug discovery process. An exciting example is the development of INS018_055, a TRAF2- and NCK-interacting kinas (TNIK) inhibitor for idiopathic pulmonary fibrosis (IPF), completed in just 18 months using PandaOmics and advanced molecular docking[38]. This AI-driven workflow combined pathway modeling, single-cell perturbation analysis, and de novo molecular docking, refining TNIK's role in fibrosis. AI-assisted docking simulations further optimized INS018_055's drug-likeness and stability, significantly expediting lead optimization. The inhibitor demonstrated strong anti-fibrotic and anti-inflammatory effects in preclinical models and rapidly progressed to a phase 1 clinical trial, highlighting the value of AI in target identification and early drug development.

MD simulations help researchers understand how proteins/peptides and drugs interact at an atomistic level in simulated dynamic biological environments[39,40]. For instance, in ocular drug discovery, MD simulations can model how a potential drug designed for the retina behaves within the aqueous humor, providing insights into the drug's binding stability and efficacy. This is especially useful for treating complex ocular conditions such as glaucoma and AMD, where drug stability and sustained efficacy are crucial. MD simulations have shown potential in guiding the design of antimicrobial peptides (or host defense peptides), revealing the secondary structures, dissecting the mechanism of action, and identifying key amino acid residues responsible for their efficacy and toxicity[35,41]. For instance, Ting et al. leveraged the atomistic insights gained from MD simulations to optimize the sequence/composition of synthetic host defense peptides,

which demonstrated potent in vivo efficacy and safety against drug-resistant bacterial keratitis[41,42].

QSAR models play a central role in this approach by leveraging molecular descriptors to predict drug-target interactions, facilitating rational drug design and lead optimization[43]. Building upon traditional QSAR, Redshaw et al. recently developed highly accurate peptide-based ML models, which could predict the structure-activity relationship of antimicrobial peptides that exhibit potent in vivo activity against *Staphylococcus aureus* bacterial keratitis[35]. This suggests that ML-based QSAR approach may accelerate the discovery of new antimicrobial therapy for treating ocular infections. DL-based QSAR (DeepQSAR) integrates DL techniques such as neural networks to enhance molecular representation and prediction accuracy[43]. For instance, generative AI (GenAI) models like SyntheMol have been developed to design novel, structurally diverse peptide-based therapeutics[44]. By leveraging a Monte Carlo tree search algorithm, SyntheMol efficiently explores vast chemical spaces to generate antimicrobial candidates that are both novel and synthesizable. Combined approach utilizing deep generative models and high-throughput MD simulations has also shown promise in accelerating antimicrobial drug discovery[45]. This strategy demonstrated remarkable speed, with two potent and low-toxicity antimicrobial peptides discovered, synthesized, and validated within just 48 days—significantly faster than conventional drug development timelines[45]. All these approaches could be adapted to enable the discovery of novel antimicrobial therapies for tackling ocular infections and antimicrobial resistance[14]. Beyond innovation, accessibility and cost-effectiveness are also key considerations in antimicrobial drug development. ZairaChem automated pipeline combines various ML models to conduct QSAR and quantitative structure-property relationship analyses on chemical libraries[46]. This approach allows for efficient prediction of drug efficacy and safety profiles, even in resource-limited settings like those in Africa.

Explainable AI (XAI) is another crucial tool for molecular discovery, as it offers transparency and interpretability in AI-driven predictions. Ocular diseases such as AMD and glaucoma involve complex molecular pathways, and XAI can enhance early-stage drug discovery by elucidating the structural and functional relationships between target proteins and small molecules. One significant advantage of XAI lies in feature attribution methods, such as Shapley Additive Explanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME), which help identify key molecular descriptors contributing to drug-target interactions[47]. This is particularly useful in understanding why certain ligand-protein interactions are favorable, providing insights into optimal drug candidates while mitigating biases inherent in black-box models[48]. One example of XAI in drug development is SmartCADD, a platform that integrates AI and quantum mechanics principles for virtual screening, improving the interpretability of docking scores and ligand binding affinity predictions[49]. Unlike traditional docking approaches, SmartCADD employs a modular, open-source framework that combines DL-based virtual screening with quantum-informed scoring functions, allowing for more precise predictions of ligand binding affinity and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. By incorporating explainability tools such as SubgraphX, SmartCADD enhances interpretability by visualizing key molecular substructures that influence binding interactions, facilitating more informed decision-making in drug optimization.

More recently, the advent of reasoning-based models like OpenAI o1, Google Gemini, and DeepSeek R1 represents another leap in AI's capability for complex problem-solving[50–52]. While these models do not yet have specific applications in drug discovery, their potential to reason through complex biochemical interactions, optimize multi-objective problems, and generate novel hypotheses makes them an exciting frontier. Future developments may enable these models to rationalize AI-generated predictions in drug discovery, interpret omics data more effectively, or even assist in multimodal drug design by integrating molecular docking, systems biology, and clinical datasets into a cohesive framework.

In vitro ADMET simulations

Once the molecular target has been established, extensive rounds of preclinical experiments and simulations are usually required to better understand the dose-response and ADMET profile before progressing to clinical trials. Traditionally, there has been a significant reliance on animal models; however, these models come with their own set of challenges, including ethical concerns, issues with cross-species extrapolation and thus high failure rates, and high costs[53].

In this context, organoids and organ-on-a-chip (OoC) technologies have emerged as promising alternatives to animal models[53]. Organoids are three-dimensional structures grown from stem cells that mimic the architecture and function of real organs[54]. OoC devices, on the other hand, are microfluidic platforms that simulate the physiological responses of entire organs. Both technologies offer more physiologically relevant systems for studying drug effects, mechanisms of action, and potential toxicity, potentially reducing reliance on animal models. While organoids and OoC technologies may not completely replace animal testing, they can help limit the number of animal groups required by offering quicker, more cost-effective, and human-relevant data. This can enhance the predictive accuracy of human drug responses, particularly in early preclinical stages.

Several OoC models have been proposed to study the retina and ocular surface, providing valuable insights into ocular drug development. A retina-on-a-chip model integrates human iPSC-derived retinal organoids (ROs) with vascular-like perfusion, allowing for the first time the recapitulation of mature photoreceptor-RPE interactions, critical for modeling retinal toxicity and drug screening[55]. Another innovative model, the Wet-AMD-on-a-chip, mimics the outer blood-retinal barrier and allows researchers to study choroidal neovascularization in a physiologically relevant manner, which is essential for testing anti-VEGF therapies[56]. Additionally, a biomimetic artificial eye model has successfully reconstructed the ocular surface, complete with blinking and tear film dynamics, enabling disease modeling for dry eye disease and high-content drug screening[57]. These models represent significant strides in ophthalmic research by bridging the gap between in vitro and in vivo systems, improving drug discovery, toxicity assessment, and therapeutic development.

The integration of AI with OoC can significantly further enhance the potential of existing technology. One of the primary benefits of AI in OoC technology is its ability to handle and analyze the large datasets generated by these systems. DL models can process data from various sensors and imaging modalities, providing detailed insights into cellular responses and drug efficacy. This is particularly beneficial for studying complex ocular diseases, where traditional methods struggle to capture the intricate ocular microenvironment. For instance, AI has been successfully applied to angiogenesis, an essential component of diabetic retinopathy, in OoCs by using DL for vessel segmentation and quantification[58]. Additionally, AI also supports the automation of experimental procedures in OoCs, enhancing reproducibility and throughput[59]. Recent advancements have enabled reinforcement learning algorithms to autonomously optimize microfluidic conditions, dynamically adjusting flow rates and culture environments to enhance cell viability and mimic physiological conditions[59]. An automated microfluidic platform has already demonstrated the ability to precisely control drug dosing and sequencing for improved treatment outcomes in pancreatic tumor organoids[60]. Recent advances have also demonstrated the emerging role of AI in enabling phenotype-based, high-throughput screening in 3D organoid systems. For example, AI-driven interferometry and machine learning-based segmentation allow for dynamic, label-free quantification of treatment responses in thousands of individual organoids at single-organoid resolution[61]. Similarly, 3D convolutional neural networks such as Stardist-3D have enabled cellular-resolution phenotyping of retinal organoids by distinguishing subclonal responses and spatial architecture[62]. These approaches go beyond traditional endpoints to capture subtle, heterogeneous drug effects in complex tissues. Applying similar AI-integrated approaches to retinal or ocular organoids could significantly improve the throughput and precision of ophthalmic drug discovery, by enabling phenotype-based screening and optimizing microfluidic flow for

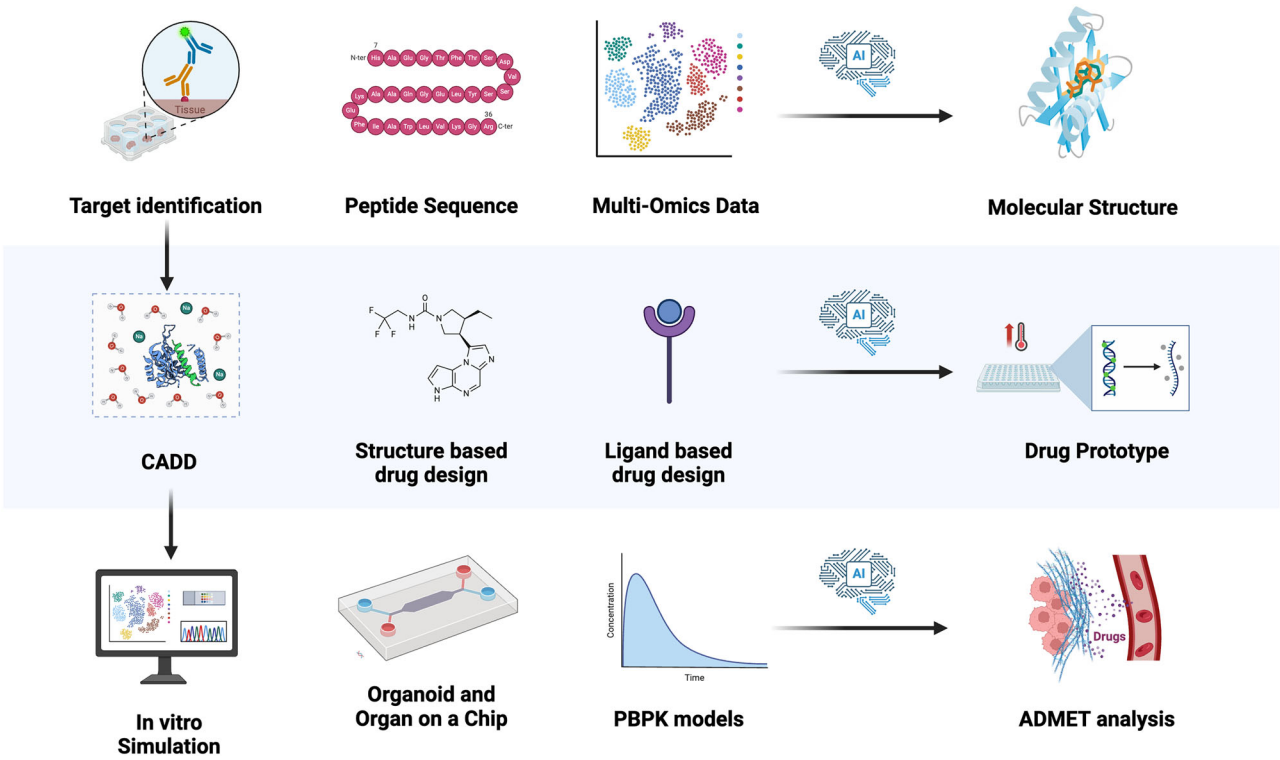

Fig. 3 | Artificial intelligence in molecular drug discovery. This figure summarizes how AI accelerates the molecular discovery process across several key steps. Beginning with target identification, AI integrates peptide sequences, multi-omics data, and molecular structure prediction to prioritize potential drug targets. CADD further enables structure-based and ligand-based drug design to develop and refine drug prototypes. AI also enhances in vitro simulation through advanced platforms like organoids, organ-on-a-chip systems, and PBPK modeling. These simulations inform early ADMET analysis, improving the prediction of a compound's behavior in humans. AI artificial intelligence, CADD computer-assisted drug design, ADMET absorption, distribution, metabolism, excretion, and toxicity, PBPK physiologically-based pharmacokinetics. Figure created with BioRender.com.

intraocular drug delivery and disease modeling—ultimately allowing for more precise, functionally relevant, and effective treatments.

Physiologically-based pharmacokinetics (PBPK) modeling is another valuable tool in preclinical studies. It predicts the ADMET of drugs in the body. PBPK models are comprised of complex parametric mathematical models that simulate the behavior of drugs within various biological compartments[63,64]. Accurate physiological and biochemical parameters are crucial for these models to make precise predictions, but obtaining such parameters can be challenging due to biological variability and limitations in experimental data. The sophisticated physiological structures, distinctive barriers, complicated biomechanical processes, and diverse delivery routes make deriving such parameters even more difficult for the eye[65]. For instance, the ocular surface presents several physiological barriers, such as the tear film, blinking, tear drainage, and structural barriers such as corneal and conjunctival epithelium. Additionally, the choice of drug delivery routes —including intravitreal, subconjunctival, and intracameral injections—can significantly influence a drug's ADME profile and therapeutic outcomes[66]. As such, animal models are often required to validate the findings observed in in vitro settings[67].

To address these challenges and reduce reliance on animal testing, AI offers a powerful alternative for simulating intricate ocular pharmacokinetic processes. For example, it can model corneal permeability by integrating drug physicochemical properties and formulation data, predict intraocular distribution across compartments like the vitreous humor and posterior segment using imaging and anatomical datasets, and anticipate ocular metabolism by identifying relevant enzymatic pathways and turnover rates. These capabilities are especially valuable for optimizing drug delivery strategies, improving ocular bioavailability, and enabling the development of next-generation ophthalmic therapeutics. This can be achieved through several key mechanisms. Firstly, AI algorithms have been widely used for data mining, enabling them to derive key physiological and biochemical parameters more precisely than traditional methods[68]. By ensuring more reliable parameter estimates, AI contributes to more accurate simulations and predictions, facilitating better drug development decisions. Secondly, AI contributes to the development of innovative ML-based, nonparametric methods[68]. Unlike traditional parametric models that are limited by fixed assumptions, nonparametric AI models can adapt to new data, learning complex patterns and relationships that may not be immediately apparent. This flexibility allows them to provide more accurate predictions for novel drugs, particularly those with unique or poorly understood properties. A real-life worked example is the application of Neural-ODE models in predicting treatment regimen for trastuzumab emtansine, a drug for breast cancer, and research efforts based on novel structures like long short-term memory networks are undergoing[69,70]. Different areas of AI applications in drug discovery are summarized in Fig. 3.

Development phase

Biomarkers for response monitoring

Recent advancements in high-throughput sequencing and single-cell analysis have significantly enhanced our understanding of the molecular impacts of drugs, providing a robust foundation for targeted therapeutic interventions. The depth of molecular insights gained, particularly concerning the physiological effects of drugs, allows for dynamic and adaptive enrollment strategies in clinical trials, potentially maximizing success rates. For instance, whole genome sequencing can be employed to stratify patients based on their genotypic variations, enabling more personalized medicine approaches and improving treatment efficacies[71]. Unlike conventional pharmacogenomics, which focuses on single nucleotide polymorphisms, AI facilitates network pharmacology by investigating the complex dynamic networks of gene-gene and gene-environment interactions that affect drug

responses[72]. Moreover, substantial efforts have been directed toward studying drug-omics associations, which can effectively decode the intricate interactions between drugs and biomolecules[73].

The eye presents unique opportunities for leveraging such technologies due to its highly specific molecular biomarkers, including proteins, DNA, and metabolites from tears, aqueous humor, and vitreous humor. In contrast to systemic biomarkers, ocular biomarkers provide a more precise understanding of the ocular microenvironment since they are locally enriched. These biomarkers can be accessed through liquid biopsies, a method that has proven to be not only insightful for understanding underlying disease mechanisms but also safe for patients[74]. Liquid biopsy techniques in ophthalmology allow for the detection and analysis of these biomarkers with minimally invasive procedures, offering a real-time snapshot of the molecular landscape within the eye[75]. This approach enhances the ability to monitor disease progression and response to treatment making it an indispensable tool in developing new therapeutic strategies. For instance, various complement factors from aqueous humor are closely associated with the pathophysiology of AMD and glaucoma, thus serving as potential treatment targets[76].

Furthermore, improvements in computational power have enabled a systems biology approach that encompasses various "omic" biomarkers, including epigenomic, transcriptomic, proteomic, lipidomic, and metabolomic data, thereby providing a more holistic perspective on pathophysiology. Researchers have constructed transcriptome and proteomic networks for both healthy and diseased eyes (e.g. diabetic retinopathy) to create a more comprehensive understanding of these conditions[77,78]. With AI, it is now possible to identify cellular mechanisms underlying eye aging, which could pave the way for novel therapeutic interventions[79]. Proteomic biomarkers also are being used to analyze responses to treatments for geographic atrophy[80]. However, a key challenge in leveraging omics data is mitigating confounding factors that obscure true biological signals. CODE-AE (context-aware deconfounding autoencoder) addresses this by disentangling intrinsic biomarkers from technical and biological noise, such as batch effects or patient variability, through a specialized self-supervised learning framework[81]. By learning shared biological patterns while suppressing dataset-specific distortions, CODE-AE improves model robustness in predicting patient-specific drug responses. Applying similar AI-driven strategies to ophthalmology could enhance precision medicine approaches for ocular diseases, improving biomarker-based diagnostics and therapeutic targeting. As our understanding of the molecular basis of eye diseases expands, AI-driven approaches are expected to play a crucial role in the discovery and development of new ophthalmic drugs by incorporating multi-omics and genomics to better predict individual outcomes and responses, ultimately improving patient outcomes and advancing the field of ocular therapeutics.

In the domain of ocular diagnostics, imaging technologies hold an even more significant place than molecular assays. Technologies such as color fundus photography, fluorescein angiography, optical coherence tomography (OCT), and OCT angiography are imperative for detailed ocular examination, and next-generation investigational modalities leveraging visible light OCT, fluorescence and multispectral imaging, and other new technologies can gather even deeper datasets on ocular and particularly retinal structure, function, metabolism, and physiology[82–84]. AI algorithms enhance the capabilities of these imaging methods by providing fast and accurate analysis of key features associated with diseases, such as vasculature and layer thickness[85,86]. This level of quantification is both highly reliable and precise, reducing the reliance on human graders, saving time, and speeding up diagnostic processes[87]. Recently, unsupervised learning and advent of vision-language model has enabled AI to discover similar patterns among diseased patients without specific pre-defined labels or domain expertise[88]. This ability brings the understanding of disease morphology to a higher level, as the algorithm can detect nuanced changes that humans cannot see, such as those in AMD, sarcoidosis and even some rare retinal conditions[88–90].

Similarly, AI can be utilized to quantify structural changes in response to treatment and detect subclinical changes that may not be visible at first[91,92]. Therefore, AI algorithms can predict patient's response to treatment and determine treatment frequency based on the biomarkers extracted from the images[93,94]. This not only helps identify eligible patients for treatment but also maximizes treatment success rate through a more personalized, effective treatment regimen. GenAI is able to synthesize hypothetical post-treatment images, helping clinicians and patients visualize treatment responses more intuitively[95]. Moreover, AI-detected changes may serve as secondary endpoints during trials, potentially providing go/no-go decision-making support in early phase trials, speeding up the drug approval process and bringing innovations to patients sooner[96,97]. For example, in glaucoma, where understanding and preserving neural structures is as important as managing intraocular pressure (IOP), AI can analyze changes in the thickness of the retinal nerve fiber layer, moving beyond the traditional focus on IOP reduction. Newer therapeutic avenues towards neuroprotection, for example in optic neuropathies, may fully rely on such AI-derived insights from novel modalities to measure meaningful outcomes in retinal or optic nerve physiology[98,99]. This introduces a more comprehensive approach to understanding treatment response. Currently, AI has been used in various secondary analyses of existing clinical trial data and has proven its values (Table 3).

Clinical trial implementation

One of the key challenges in clinical trials has been suboptimal patient cohort selection, inefficient recruiting techniques, and difficulties in maintaining effective monitoring throughout the trial period. These challenges are major contributors to high trial failure rates. Traditional methods often rely on electronic health records (EHR) and manual processes to identify eligible participants, which can miss key patients or include those who do not meet all criteria. AI-driven predictive analytics and ML algorithms address these issues by refining patient selection and recruitment strategies, a process known as clinical trial enrichment[20]. By analyzing large datasets, including medical histories, laboratory investigations, and even lifestyle factors, AI can identify the most appropriate candidates for specific trials with greater accuracy. For instance, AI algorithms based on OCT scans have demonstrated higher precision in identifying eligible patients for AMD clinical trials compared to conventional EHR systems alone, improving the representativeness and appropriateness of the patient cohort[100].

Moreover, AI facilitates the operation of decentralized clinical trials, which allow participants to engage in the study from various locations, not limited to a few centralized trial sites[101]. This approach significantly expands the participant pool, particularly for diseases like AMD and diabetic retinopathy, which predominantly affect elderly populations who may have mobility constraints. Furthermore, AI enables cross-center collaboration by allowing multiple trial sites to share insights and data in real-time through techniques like federated learning. Federated learning supports the analysis of aggregated data from different trial sites without compromising patient privacy, as individual data remains localized[102]. This helps address data privacy concerns while also improving the robustness of trial outcomes by drawing on a larger, more diverse dataset.

Adaptive trial designs supported by AI further enhance the efficiency of clinical trials. In traditional trials, protocols are often static and predetermined, which can lead to delays or resource waste if the initial hypotheses prove ineffective. AI-driven adaptive trials dynamically adjust protocols based on interim results, allowing researchers to focus resources on the most promising therapeutic avenues while discontinuing less effective treatments earlier in the process[103]. These platforms also streamline trial management by automating tasks such as data entry, and adverse event reporting, and patient follow-up, increasing the overall efficiency and accuracy of trials. This not only speeds up the trial but also reduces the financial burden associated with lengthy and ineffective studies. There have already been studies incorporating AI into clinical design in real life. Real-world examples of AI integration in clinical design are already emerging. For instance, the Vibe Up study is a decentralized AI-adaptive group sequential

Table 3 | A selected summary of the current studies using deep learning for secondary analysis of clinical trial data or design of clinical trials in ophthalmology

Author name (year)	Study population	Sample size	Treatment	Condition	Imaging	Outcome of interest
Quantify structural changes						
Schmidt-Erfurth et al.[148]	HAWK and HARRIER	1078 and 739	Brolucizumab OR Aflibercept	nAMD	OCT	IRF, SRF, PED
Fu et al.[149]	FILLY	197	Pegcetacoplan	GA	OCT	GA area, RPE loss, hypertransmission, PR degeneration, and intact macular area
Vogl et al.[150]	FILLY	312	Pegcetacoplan	GA	OCT	LPR, PR thickness, HRF concentration
Roberts et al.[151]	DRCR Network	570	Aflibercept, Ranibizumab, OR Bevacizumab	DME	OCT	IRF, SRF
Schmidt-Erfurth et al.[152]	OAKS and DERBY	897	Pegcetacoplan	GA	OCT	RPE loss and PR degeneration
Predicting functional restoration						
Mulyukov et al.[153]	HAWK and HARRIER	594 + 389	Brolucizumab OR Aflibercept	nAMD	OCT	Disease activity score
Chandra et al.[154]	CATT	1029	Ranibizumab OR Bevacizumab	nAMD	OCT	BCVA
Kikuchi et al.[155]	AVENUE	273	Faricimab	nAMD	OCT	BCVA and CST
Maunz et al.[156]	HARBOR	432	Ranibizumab	nAMD	OCT	BCVA
Predicting treatment frequency						
Bogunović et al.[157]	HARBOR	317	Ranibizumab	nAMD	OCT	Low (≤5 injection), High (≥16)
Chandra et al. [158]	CATT	493	Ranibizumab OR Bevacizumab	nAMD	OCT	Low (≤8), High (≥19)

nAMD neovascular age-related macular degeneration, *GA* geographical atrophy, *DME* diabetic macular edema, *OCT* optical coherence tomography, *IRF* intraretinal fluid, *SRF* subretinal fluid, *PED* pigment epithelial detachment, *RPE* retinal pigment epithelium, *PR* photoreceptor, *LPR* local progression rate, *HRF* hyperreflective foci, *BCVA* best corrected visual acuity, *CST* central subfield thickness.

randomized controlled trial that compares the effectiveness of digital self-guided interventions in reducing self-reported psychological distress[104]. Unlike traditional randomized controlled trials (RCTs), which require fixed treatment allocations, Vibe Up employs a bandit-based response adaptive trial method, meaning that as new data emerges, the AI system dynamically adjusts participant allocation to prioritize the most effective interventions. This AI-driven approach not only reduces sample size requirements but also improves efficiency by optimizing treatment allocation in real time, demonstrating how adaptive methodologies can make clinical trials more responsive and cost-effective.

Additionally, the integration of AI-generated Digital Twins into clinical trials is revolutionary. Digital Twins are AI-driven virtual representations of trial participants, constructed from real-world clinical data, including biometrics, imaging, genomics, and molecular markers[105]. Digital Twins are revolutionizing clinical trial efficiency by reducing the reliance on large control groups, enabling adaptive trial designs, and predicting treatment responses with greater accuracy[106]. Traditionally, RCTs require large control arms, where participants receive a placebo or standard-of-care treatment. However, AI-powered Digital Twins can generate synthetic control arms—statistical representations of placebo groups derived from historical clinical trial data—thereby reducing the number of real patients needed in these groups. This minimizes ethical concerns associated with withholding treatment from participants and accelerates trial timelines. Additionally, Digital Twins enable prognostic covariate adjustment (PROCOVA), an AI-driven statistical method that improves trial efficiency by enhancing statistical power[105]. This technique has been qualified by the European Medicines Agency (EMA) and aligns with existing FDA guidelines, allowing for smaller, more efficient trials while maintaining rigorous scientific standards[105]. Furthermore, AI-driven Digital Twins continuously update with new biomarker data, refining predictions of individual treatment responses. In ophthalmology, for example, Digital Twins could integrate multi-modal imaging, molecular biomarkers, and AI-driven risk models to stratify patients based on their likelihood of responding to treatment. This enables adaptive trial designs, where treatment regimens are dynamically adjusted based on real-time patient response data[106]. In ophthalmology, Digital Twin applications are beginning to take shape across multiple disease areas. For instance, in proliferative vitreoretinopathy, Digital Twins have been proposed to model the disease's complex fibrotic pathways and simulate responses to anti-fibrotic agents such as Nintedanib[107]. Similarly, in glaucoma, Digital Twins can incorporate multimodal clinical data—including intraocular pressure, optic nerve imaging, and genetic risk factors—to forecast disease progression and support personalized treatment planning[108]. By integrating patient-specific molecular and imaging data, these models can predict therapeutic efficacy and help optimize treatment regimens without the need for extensive in vivo testing.

The integration of DL algorithms with smartphone technology and wearable devices further simplifies the trial process by making monitoring more accessible and user-friendly[109,110]. Smartphones equipped with AI-based diagnostic tools can facilitate regular ocular health monitoring by patients themselves, enabling continuous data collection throughout the trial. This not only empowers patients to take a more active role in their healthcare but also provides real-time data to pharmaceutical companies and researchers. The ability to monitor drug performance more closely allows for timely adjustments to treatment protocols, thereby improving the overall effectiveness of clinical trials. For instance, a study conducted in China demonstrated that patients managed by a combination of primary care providers and LLMs had better self-management behavior and adherence to follow-up care for diabetic retinopathy treatment compared to those managed by primary care providers alone[111]. This improvement is likely due to LLM's ability to provide more personalized and data-driven recommendations, while also offering structured guidance that enhances communication and decision-making between patients and providers. Additionally, LLM-generated responses may improve patient engagement by increasing trust and accessibility of medical information. Such advancements highlight the expanding role of AI in enhancing diagnostic

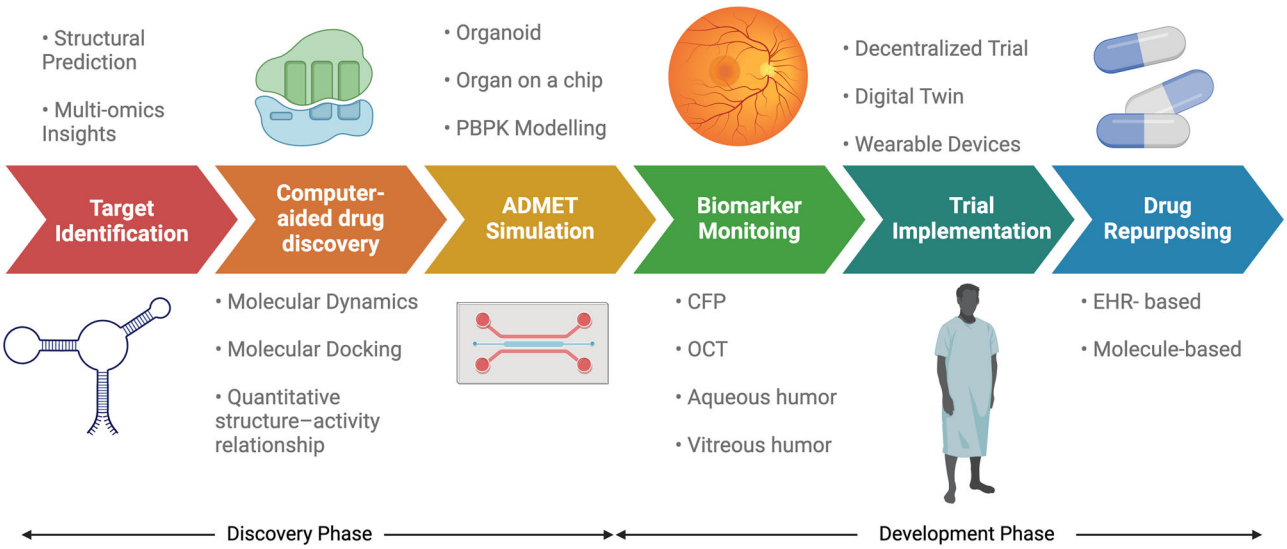

Fig. 4 | Applications of artificial intelligence and digital health across the drug development pipeline. In the discovery phase, AI supports target identification through structural prediction and multi-omics integration, and enhances computer-aided drug design via molecular modeling and docking. ADMET simulation benefits from organoids, organ-on-a-chip systems, and PBPK modeling. During development, biomarker monitoring incorporates ocular imaging (e.g., CFP, OCT) and fluid-based biomarkers (aqueous and vitreous humor) for evaluating treatment response. Trial implementation is advanced by decentralized designs, digital twins, and wearable technologies. Finally, drug repurposing leverages AI using EHR data and molecular analytics to identify new uses for existing therapies. ADMET absorption, distribution, metabolism, excretion, and toxicity, PBPK physiologically-based pharmacokinetics, CFP colored fundus photography, OCT optical coherence tomography, EHR electronic health records. Figure created with BioRender.com.

accuracy and treatment efficacy in ophthalmology, paving the way for more personalized and effective healthcare solutions.

Post-market drug repurposing

Drug development is indeed a time-consuming and expensive process. In this context, the repurposing of existing, proven-safe drugs for new therapeutic uses offers a compelling alternative[112]. This approach not only saves time and reduces costs significantly but also minimizes risk, as the safety profiles of these drugs are already well-understood. Additionally, drug repurposing can expedite the availability of treatments, particularly in response to urgent health crises where new drug discovery and approval might be too slow. It also extends the commercial life of drugs, providing pharmaceutical companies with new markets and patients with more treatment options. In today's era of big data and extensive data sharing, the use of AI in drug repurposing is increasingly viable and valuable. AI can integrate and analyze diverse data types from global datasets, offering insights that might not be apparent through traditional research methods. This technological approach is becoming an integral part of the pharmaceutical industry's strategy to enhance drug development efficiency and responsiveness to emerging health challenges.

Natural language processing and DL are pivotal in identifying repurposing opportunities by extrapolating from vast amounts of existing data, including published research, clinical trial data, and EHR. Various studies confirmed its feasibility in conditions like coronary artery disease, Alzheimer's disease, and Parkinson's disease, and such capability was most notably demonstrated during the COVID-19 pandemic[113,114]. Remdesivir, an antiviral drug initially designed for the Ebola virus, was identified by a DL model as one of the potential treatments for COVID-19[114]. Subsequent clinical trials also confirmed its benefits, leading to emergency use authorization by regulatory bodies worldwide[115]. This real-life example showcased how AI could leverage big data to identify potential drug repurposing candidates effectively. Recently, advances in GenAI, particularly LLMs like ChatGPT, have pushed the limits of AI in drug repurposing to new heights[18,116,117]. GenAI excels at processing unstructured data and can identify non-obvious connections, making it an invaluable tool in drug discovery and repurposing. Despite its recent emergence, researchers have already applied GenAI to identify potential drug-repurposing candidates for Alzheimer's disease[118]. Although there have not yet been eye-specific applications, it is only a matter of time before GenAI is utilized in ophthalmic research and drug discovery.

In addition to leveraging real-world efficacy data from EHRs, repurposing can also be guided by AI-powered omics-based approaches. Recent studies have demonstrated that combined multi-omics with AI-driven computational modeling can enhance drug discovery and repositioning. For instance, AI-based omics analysis has been applied to identify drug pairs for pyroptosis therapy in triple-negative breast cancer, integrating transcriptomic data, drug databases, and biofactor-regulated neural networks[119]. Similar methodologies could be employed in ophthalmology, identifying systemic drugs with beneficial effects on eye diseases. Figure 4 summarizes the AI applications throughout the entire phase of drug discovery and development.

Limitations

Regulatory considerations

While AI holds great potential in revolutionizing drug discovery, it also comes with limitations. Given the extensive data requirements for training AI systems, concerns about data privacy and security have emerged[120]. Data sharing across institutions, countries or industries often leads to exposure risks of sensitive health data. Regulations such as the General Data Protection Regulation and the Health Insurance Portability and Accountability Act should be adhered to protect patient confidentiality and privacy. A promising solution to address these concerns is federated learning, a technique which enables raw data to remain with its source, thereby minimizing the risk of exposure. Clients train local ML models on their own data, sending only updated model parameters to a central server for aggregation[121]. The server then shares aggregated parameters back with clients for further training. This process repeats until the model achieves the desired accuracy[121]. By facilitating collaboration between AI models, federated learning can enhance data privacy while contributing to the development of more accurate ML models in drug discovery, such as Alphafold and complementary technologies such as OoC.

The United States Food and Drug Administration's (FDA) has led efforts to regulate AI in drug discovery, given its implications on treatment and prognosis. The FDA has reviewed hundreds of regulatory submissions

involving AI in drug development. In March 2024, it introduced a risk-based regulatory framework outlining four areas of focus: (1) fostering collaboration to safeguard public health; (2) promoting development of harmonized standards, guidelines, best practices, and tools; (3) advancing the development of regulatory approaches that support innovation; and (4) supporting research related to evaluation and monitoring of AI performance[122]. Globally, the EMA and the Medicines and Healthcare products Regulatory Agency (MHRA) are developing standardized protocols for AI and ML in drug discovery. Regulatory frameworks struggle to keep pace with AI's rapid evolution. Current drug discovery regulations lack provisions for GenAI and LLMs, which tend to produce unpredictable outputs and challenges[123]. These regulations should extend to AI and bioinformatics for analysis of aqueous or vitreous humor biomarkers to uphold ethical standards in AI usage in drug development. Currently, there lacks a unified international guideline. A coordinated and global effort for more consistent and united regulations for applying AI in drug discovery are needed[124]. Additionally, a life cycle management approach—monitoring AI models post-market—could improve implementation but remains difficult to enforce[123].

AI's role in drug discovery raises complex patentability and intellectual property concerns. The United States Patent and Trademark Office allows patents for "any new and useful process", but algorithms, as abstract procedures, may not qualify[125]. This is further complicated by the Patient Eligibility Restoration Act of 2023 which excludes mental processes and mathematical formulas from eligibility[125]. Concerns regarding the originality of AI-aided or AI-generated therapeutics have been raised. Under the Federal Circuit, an inventor must be a natural person, hence an AI algorithm cannot be a named inventor[126]. Enablement and written description requirements in section 112 have been hinderances, especially when vague descriptions of "ML" and "neural networks" have been used without specific details of the method. To avoid these issues, the specification should aim to contain a written description of the invention in a way that it is understandable, full, clear and concise[126,127].

Challenges in ethical and reliable AI

Transparency and explainability are crucial for regulatory approval and clinical adoption[124]. Lack of transparency and interpretability in AI models, particularly black-box systems, complicates the adoption and fostering of trust in employing AI in drug development[128,129]. Explainability refers to the AI's ability to clarify its decision-making process and bias mitigation methods in a manner that is comprehensible to humans[120]. This transparency facilitates the determination of liability in cases of adverse outcomes. This transparency is especially vital in clinical trials, where regulatory bodies must understand AI-driven predictions to assess their validity and ensure patient safety. Without clear explanations, AI-generated drug candidates may face increased scrutiny, delaying trial approvals and regulatory acceptance[130]. While regulations remain underdeveloped, guidelines such as DECIDE-AI, SPIRIT-AI and CONSORT-AI provide structured reporting frameworks to enhance accountability in AI-driven clinical research[131–133]. However, these guidelines primarily focus on AI applications in disease diagnosis rather than drug development. The increasing integration of AI into drug development underscores the urgent need for algorithmic inclusivity and transparency. Policymakers must attempt to translate these guidelines to standardized regulations to protect patients from associated risks.

The quality and efficiency of AI-led drug discovery are heavily contingent on data reliability, representativeness and diversity. Limited or inconsistent training data can impair model performance by misrepresenting the molecular structure of drugs[134]. Even minor alterations in chemical structure can significantly impact binding affinity, pharmacokinetics and pharmacodynamics, potentially rendering therapies ineffective or toxic[134]. Several solutions may be considered to overcome these challenges. Firstly, a centralized biomarker repository with standardized and nationally representative data may minimize inconsistencies and improve representation[124]. Secondly, transfer learning, which applies knowledge from related tasks, can improve learning efficiency with limited datasets. Thirdly, GenAI models, such as generative adversarial networks (GANs) and variational autoencoder (VAEs), can generate synthetic data to overcome data scarcity. For example, MedGAN, a DL model combining GANs and graph convolutional networks facilitates the generation of new quinoline-scaffold molecules[135]. This approach may be particularly attractive for rare ophthalmic diseases, where real-world data are limited and synthetic augmentation could help improve dataset diversity. However, GANs also bring their own set of challenges, including the risk of generating biologically irrelevant or harmful compounds, limitations in transparency and subsequent regulatory acceptance, amplified bias, and training instability. Without rigorous validation, synthetic data may inadvertently reinforce existing biases or produce misleading outputs—especially in disease areas with incomplete biological understanding. These risks highlight the need for transparency, oversight, and cautious interpretation in applying synthetic data to rare disease research. Without a standardized approach to integrating AI-generated candidates into established drug pipelines, regulatory acceptance will remain a significant barrier.

Ensuring equitable and ethical use of AI in drug development is another key consideration. AI models can inadvertently perpetuate bias and discrimination[124]. For instance, VisionFM, a foundation model that fosters multiple AI applications including ophthalmological diagnosis and biomarker identification, was pretrained on a dataset disproportionately representing the Chinese population[88]. Consequently, it may fail to capture the heterogeneity of rare conditions such as Leber hereditary optic neuropathy, Best disease and Bietti Crystalline Dystrophy[136]. If such biases extend to AI-driven drug discovery, they could result in therapies that are less effective for underrepresented populations, ultimately skewing clinical trial results and limiting the generalizability of findings[137]. Moreover, access to cutting-edge AI tools and computational infrastructure remains uneven across regions, impacting low- and middle-income countries (LMICs) the most, hindering their ability to participate in AI-driven research. This exacerbates healthcare inequity where AI-generated treatments may fail to adequately address the health needs of these populations. LMICs often face systemic barriers—such as fragmented health systems, limited biobank access, and underrepresentation in genomic datasets—which further restrict their participation in AI-driven biomedical research and innovation[138]. Bias in training data can also impact participant selection in AI-optimized trial recruitment, leading to skewed demographic representation and potentially confounded results. Current AI-assisted recruitment strategies have shown promise in streamlining patient matching based on eligibility criteria, yet they often rely on EHRs that may underrepresent certain populations. Similarly, digital twins must be constructed using high-quality, representative datasets. If built on biased or incomplete data, digital twins may yield misleading predictions, potentially leading to erroneous trial designs or ineffective drug candidates. Data augmentation offers a potential solution by generating synthetic data and enhancing data diversity, thereby mitigating discrimination in AI-powered drug discovery. However, data augmentation alone cannot fully address biases; robust validation protocols and continuous monitoring are necessary to ensure fairness and accuracy in clinical trials[137].

As AI increasingly shapes drug discovery, regulatory updates must address these emerging applications[139]. Given AI's transformative impact, industry stakeholders must enhance quality assessment beyond FDA oversight[123]. Ensuring equity in AI-driven drug development, establishing patent frameworks, and promoting transparency will be critical to widespread adoption.

Conclusions

AI has a huge potential to transform drug discovery and development, offering groundbreaking opportunities in molecular drug target identification, preclinical and clinical testing, and drug repurposing. However, the ethical and societal complexities inherent in this technology necessitate careful and deliberate strategies to fully leverage its benefits[120]. As AI continues to evolve, it is essential to stay informed about emerging developments and implement responsible practices to ensure equitable benefits for all patients[120].

Data Availability

No datasets were generated or analysed during the current study.

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References

1. Sertkaya, A., Beleche, T., Jessup, A. & Sommers, B. D. Costs of drug development and research and development intensity in the US, 2000-2018. *JAMA Netw. Open* **7**, e2415445 (2024).
2. Spherical Insights LLP. Global Ophthalmic Drugs Market Size, Share, and COVID-19 Impact Analysis, by Disease, Drug Class, Dosage, Administration, Product, and Region, Forecast to 2030. (published February 2023; accessed 20 August 2025).
3. Scott, I. U. et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* **114**, 1860–1867 (2007).
4. Rosenfeld, P. J., Moshfeghi, A. A. & Puliafito, C. A. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg. Lasers Imaging* **36**, 331–335 (2005).
5. Cheung, N., Mitchell, P. & Wong, T. Y. Diabetic retinopathy. *Lancet* **376**, 124–136 (2010).
6. Wong, T. Y., Cheung, C. M. G., Larsen, M., Sharma, S. & Simó, R. Diabetic retinopathy. *Nat. Rev. Dis. Prim.* **2**, 16012 (2016).
7. Mitchell, P., Liew, G., Gopinath, B. & Wong, T. Y. Age-related macular degeneration. *Lancet* **392**, 1147–1159 (2018).
8. Bloch, S. B., Larsen, M. & Munch, I. C. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am. J. Ophthalmol.* **153**, 209–213.e202 (2012).
9. Israeli, A., Peer, H., Gleitman, I., Falick, Y. & Mezer, E. Time trends of etiologies of blindness in Israel 2009-2020: have methods to decrease leading causes of blindness been exhausted?. *Am. J. Ophthalmol.* **240**, 149–158 (2022).
10. Russell, S. et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet* **390**, 849–860 (2017).
11. Bourne, R. R. A. et al. The UK clinical eye research strategy: refreshing research priorities for clinical eye research in the UK. *Eye* **38**, 1947–1957 (2024).
12. Burki, T. A new paradigm for drug development. *Lancet Digit. Health* **2**, e226–e227 (2020).
13. Stokes, J. M. et al. A deep learning approach to antibiotic discovery. *Cell* **180**, 688–702.e613 (2020).
14. Ho, C. S. et al. Antimicrobial resistance: a concise update. *Lancet Microbe* **6**, 100947. https://doi.org/10.1016/j.lanmic.2024.07.010 (2025).
15. Mock, M., Edavettal, S., Langmead, C. & Russell, A. AI can help to speed up drug discovery—but only if we give it the right data. *Nature* **621**, 467–470 (2023).
16. Liu, Z. et al. AI-based language models powering drug discovery and development. *Drug Discov. Today* **26**, 2593–2607 (2021).
17. Jeyaraman, M. et al. ChatGPT in action: harnessing artificial intelligence potential and addressing ethical challenges in medicine, education, and scientific research. *World J. Methodol.* **13**, 170–178 (2023).
18. Thirunavukarasu, A. J. et al. Large language models in medicine. *Nat. Med.* **29**, 1930–1940 (2023).
19. Zhang, K. et al. Artificial intelligence in drug development. *Nat. Med.* **31**, 45–59 (2025).
20. Harrer, S., Shah, P., Antony, B. & Hu, J. Artificial intelligence for clinical trial design. *Trends Pharmacol. Sci.* **40**, 577–591 (2019).
21. Liao, Q. et al. Application of artificial intelligence in drug-target interactions prediction: a review. *npj Biomed. Innov.* **2**, 1 (2025).
22. Sadybekov, A. V. & Katritch, V. Computational approaches streamlining drug discovery. *Nature* **616**, 673–685 (2023).
23. Weinberg, J., Gaur, M., Swaroop, A. & Taylor, A. Proteostasis in aging-associated ocular disease. *Mol. Asp. Med.* **88**, 101157 (2022).
24. Venkatraman, A., Duong-Thi, M. D., Pervushin, K., Ohlson, S. & Mehta, J. S. Pharmaceutical modulation of the proteolytic profile of Transforming Growth Factor Beta induced protein (TGFBIp) offers a new avenue for treatment of TGFBI-corneal dystrophy. *J. Adv. Res.* **24**, 529–543 (2020).
25. Burley, S. K. et al. Protein Data Bank: a comprehensive review of 3D structure holdings and worldwide utilization by researchers, educators, and students. *Biomolecules* **12**, https://doi.org/10.3390/biom12101425 (2022).
26. Senior, A. W. et al. Improved protein structure prediction using potentials from deep learning. *Nature* **577**, 706–710 (2020).
27. Jumper, J. et al. Highly accurate protein structure prediction with AlphaFold. *Nature* **596**, 583–589 (2021).
28. Abramson, J. et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature* **630**, 493–500 (2024).
29. Zhang, Z. et al. Structure prediction of novel isoforms from uveal melanoma by AlphaFold. *Sci. Data* **10**, 513 (2023).
30. Kamya, P. et al. PandaOmics: an AI-driven platform for therapeutic target and biomarker discovery. *J. Chem. Inf. Model.* **64**, 3961–3969 (2024).
31. Wan, F., Torres, M. D. T., Peng, J. & de la Fuente-Nunez, C. Deep-learning-enabled antibiotic discovery through molecular de-extinction. *Nat. Biomed. Eng.* **8**, 854–871 (2024).
32. Maasch, J., Torres, M. D. T., Melo, M. C. R. & de la Fuente-Nunez, C. Molecular de-extinction of ancient antimicrobial peptides enabled by machine learning. *Cell Host Microbe* **31**, 1260–1274.e1266 (2023).
33. Torres, M. D. T. et al. Mining human microbiomes reveals an untapped source of peptide antibiotics. *Cell* **187**, 5453–5467.e5415 (2024).
34. Santos-Júnior, C. D. et al. Discovery of antimicrobial peptides in the global microbiome with machine learning. *Cell* **187**, 3761–3778.e3716 (2024).
35. Redshaw, J., Ting, D. S. J., Brown, A., Hirst, J. D. & Gärtner, T. Krein support vector machine classification of antimicrobial peptides. *Digital Discov.* **2**, 502–511 (2023).
36. Gentile, F. et al. Deep docking: a deep learning platform for augmentation of structure based drug discovery. *ACS Cent. Sci.* **6**, 939–949 (2020).
37. Luttens, A. et al. Rapid traversal of vast chemical space using machine learning-guided docking screens. *Nat. Comput. Sci*. https://doi.org/10.1038/s43588-025-00777-x (2025).
38. Ren, F. et al. A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-024-02143-0 (2024).
39. Hollingsworth, S. A. & Dror, R. O. Molecular dynamics simulation for all. *Neuron* **99**, 1129–1143 (2018).
40. Prašnikar, E., Ljubič, M., Perdih, A. & Borišek, J. Machine learning heralding a new development phase in molecular dynamics simulations. *Artif. Intell. Rev.* **57**, 102 (2024).
41. Ting, D. S. J. et al. Evaluation of host defense peptide (CaD23)-antibiotic interaction and mechanism of action: insights from experimental and molecular dynamics simulations studies. *Front. Pharmacol.* **12**, https://doi.org/10.3389/fphar.2021.731499 (2021).
42. Ting, D. S. J., Lakshminarayanan, R., Mohammad, I. & Dua, H. Development of novel human-derived hybrid host defense peptides for infectious keratitis. *BMJ Open Ophthalmol.* **8**, (2023).
43. Tropsha, A., Isayev, O., Varnek, A., Schneider, G. & Cherkasov, A. Integrating QSAR modelling and deep learning in drug discovery: the emergence of deep QSAR. *Nat. Rev. Drug Discov.* **23**, 141–155 (2024).

44. Swanson, K. et al. Generative AI for designing and validating easily synthesizable and structurally novel antibiotics. *Nat. Mach. Intell.* **6**, 338–353 (2024).
45. Das, P. et al. Accelerated antimicrobial discovery via deep generative models and molecular dynamics simulations. *Nat. Biomed. Eng.* **5**, 613–623 (2021).
46. Turon, G. et al. First fully-automated AI/ML virtual screening cascade implemented at a drug discovery centre in Africa. *Nat. Commun.* **14**, 5736 (2023).
47. Alizadehsani, R. et al. Explainable artificial intelligence for drug discovery and development: a comprehensive survey. *IEEE Access* **12**, 35796–35812 (2024).
48. Jiménez-Luna, J., Grisoni, F. & Schneider, G. Drug discovery with explainable artificial intelligence. *Nat. Mach. Intell.* **2**, 573–584 (2020).
49. Madushanka, A., Laird, E., Clark, C. & Kraka, E. SmartCADD: AI-QM empowered drug discovery platform with explainability. *J. Chem. Inf. Model.* **64**, 6799–6813 (2024).
50. OpenAI et al. OpenAI o1 System Card. *arXiv* https://ui.adsabs.harvard.edu/abs/2024arXiv241216720O (2024).
51. Team, G. et al. Gemini: a family of highly capable multimodal models. *arXiv* https://ui.adsabs.harvard.edu/abs/2023arXiv231211805G (2023).
52. DeepSeek-AI et al. DeepSeek-R1: incentivizing reasoning capability in LLMs via reinforcement learning. *arXiv* https://ui.adsabs.harvard.edu/abs/2025arXiv250112948D (2025).
53. Loewa, A., Feng, J. J. & Hedtrich, S. Human disease models in drug development. *Nat. Rev. Bioeng.* **1**, 545–559 (2023).
54. Shi, H. et al. Organoid intelligence: integration of organoid technology and artificial intelligence in the new era of in vitro models. *Med. Nov. Technol. Devices* **21**, 100276 (2024).
55. Achberger, K. et al. Merging organoid and organ-on-a-chip technology to generate complex multi-layer tissue models in a human retina-on-a-chip platform. *eLife* **8**, e46188 (2019).
56. Chung, M. et al. Wet-AMD on a chip: modeling outer blood-retinal barrier in vitro. *Adv. Healthc. Mater.* **7**, 1700028 (2018).
57. Seo, J. et al. Multiscale reverse engineering of the human ocular surface. *Nat. Med.* **25**, 1310–1318 (2019).
58. Choi, D.-H. et al. Analyzing angiogenesis on a chip using deep learning-based image processing. *Lab Chip* **23**, 475–484 (2023).
59. Dressler, O. J., Howes, P. D., Choo, J. & deMello, A. J. Reinforcement learning for dynamic microfluidic control. *ACS Omega* **3**, 10084–10091 (2018).
60. Schuster, B. et al. Automated microfluidic platform for dynamic and combinatorial drug screening of tumor organoids. *Nat. Commun.* **11**, 5271 (2020).
61. Tebon, P. J. et al. Drug screening at single-organoid resolution via bioprinting and interferometry. *Nat. Commun.* **14**, 3168 (2023).
62. Mukashyaka, P. et al. High-throughput deconvolution of 3D organoid dynamics at cellular resolution for cancer pharmacology with Cellos. *Nat. Commun.* **14**, 8406 (2023).
63. Kuepfer, L. et al. Applied concepts in PBPK modeling: how to build a PBPK/PD model. *CPT Pharmacomet. Syst. Pharm.* **5**, 516–531 (2016).
64. Jones, H. & Rowland-Yeo, K. Basic concepts in physiologically based pharmacokinetic modeling in drug discovery and development. *CPT Pharmacomet. Syst. Pharm.* **2**, e63 (2013).
65. Wang, N. et al. How can machine learning and multiscale modeling benefit ocular drug development?. *Adv. Drug Deliv. Rev.* **196**, 114772 (2023).
66. Kompella, U. B., Hartman, R. R. & Patil, M. A. Extraocular, periocular, and intraocular routes for sustained drug delivery for glaucoma. *Prog. Retinal Eye Res.* **82**, 100901 (2021).
67. Ting, D. S. J. et al. Hybrid derivative of cathelicidin and human beta defensin-2 against Gram-positive bacteria: a novel approach for the treatment of bacterial keratitis. *Sci. Rep.* **11**, 18304 (2021).
68. Chou, W.-C. & Lin, Z. Machine learning and artificial intelligence in physiologically based pharmacokinetic modeling. *Toxicol. Sci.* **191**, 1–14 (2022).
69. Lu, J., Deng, K., Zhang, X., Liu, G. & Guan, Y. Neural-ODE for pharmacokinetics modeling and its advantage to alternative machine learning models in predicting new dosing regimens. *iScience* **24**, 102804 (2021).
70. Liu, X. et al. Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling. *Int. J. Clin. Pharm. Ther.* **59**, 138–146 (2021).
71. Szustakowski, J. D. et al. Advancing human genetics research and drug discovery through exome sequencing of the UK Biobank. *Nat. Genet.* **53**, 942–948 (2021).
72. Zhou, W., Li, X., Han, L. & Fan, S. in *Network Pharmacology* (ed. Li, S.) 35–73 (Springer, 2021).
73. Allesøe, R. L. et al. Discovery of drug–omics associations in type 2 diabetes with generative deep-learning models. *Nat. Biotechnol.* **41**, 399–408 (2023).
74. Wolf, J. et al. Using electronic health record data to determine the safety of aqueous humor liquid biopsies for molecular analyses. *Ophthalmol. Sci.* **4**, 100517 (2024).
75. Wolf, J. et al. Liquid biopsy proteomics in ophthalmology. *J. Proteome Res.* **23**, 511–522 (2024).
76. Kato, Y. et al. Age-related maculopathy susceptibility 2 and complement factor H polymorphism and intraocular complement activation in neovascular age-related macular degeneration. *Ophthalmol. Sci.* **2**, https://doi.org/10.1016/j.xops.2022.100167 (2022).
77. Wolf, J. et al. The Human Eye Transcriptome Atlas: a searchable comparative transcriptome database for healthy and diseased human eye tissue. *Genomics* **114**, 110286 (2022).
78. Alli-Shaik, A. et al. System-wide vitreous proteome dissection reveals impaired sheddase activity in diabetic retinopathy. *Theranostics* **12**, 6682–6704 (2022).
79. Wolf, J. et al. Liquid-biopsy proteomics combined with AI identifies cellular drivers of eye aging and disease in vivo. *Cell* **186**, 4868–4884.e4812 (2023).
80. Hallam, T. M. et al. Ocular biomarker profiling after complement factor I gene therapy in geographic atrophy secondary to age-related macular degeneration. *medRxiv* https://doi.org/10.1101/2024.06.12.24308796 (2024).
81. He, D., Liu, Q., Wu, Y. & Xie, L. A context-aware deconfounding autoencoder for robust prediction of personalized clinical drug response from cell-line compound screening. *Nat. Mach. Intell.* **4**, 879–892 (2022).
82. Beykin, G., Norcia, A. M., Srinivasan, V. J., Dubra, A. & Goldberg, J. L. Discovery and clinical translation of novel glaucoma biomarkers. *Prog. Retin. Eye Res.* **80**, 100875 (2021).
83. Beykin, G. & Goldberg, J. L. Molecular biomarkers for glaucoma. *Curr. Ophthalmol. Rep.* **7**, 171–176 (2019).
84. Norcia, A. M., Yakovleva, A., Jehangir, N. & Goldberg, J. L. Preferential loss of contrast decrement responses in human glaucoma. *Invest. Ophthalmol. Vis. Sci.* **63**, 16 (2022).
85. Zhou, Y. et al. AutoMorph: automated retinal vascular morphology quantification via a deep learning pipeline. *Transl. Vis. Sci. Technol.* **11**, 12–12 (2022).
86. Moraes, G. et al. Quantitative analysis of OCT for neovascular age-related macular degeneration using deep learning. *Ophthalmology* **128**, 693–705 (2021).
87. Li, J. O. et al. Digital technology, tele-medicine and artificial intelligence in ophthalmology: a global perspective. *Prog. Retin. Eye Res.* **82**, 100900 (2021).
88. Qiu, J. et al. Development and Validation of a Multimodal Multitask Vision Foundation Model for Generalist Ophthalmic Artificial Intelligence. *NEJM AI* **1**, Aloa2300221, https://doi.org/10.1056/Aloa2300221 (2024).

89. Xiong, F. et al. Ocular signs and testing most compatible with sarcoidosis-associated uveitis: a latent class analysis. *Ophthalmol. Sci.* **4**, https://doi.org/10.1016/j.xops.2024.100503 (2024).
90. Holland, R. et al. Deep-learning-based clustering of OCT images for biomarker discovery in age-related macular degeneration (PINNACLE study report 4). *Ophthalmol. Sci.* https://doi.org/10.1016/j.xops.2024.100543 (2024).
91. Moraes, G. et al. Quantifying changes on OCT in eyes receiving treatment for neovascular age-related macular degeneration. *Ophthalmol. Sci.* **4**, https://doi.org/10.1016/j.xops.2024.100570 (2024).
92. Massengill, M. T., Cubillos, S., Sheth, N., Sethi, A. & Lim, J. I. Response of diabetic macular edema to anti-VEGF medications correlates with improvement in macular vessel architecture measured with OCT angiography. *Ophthalmol. Sci.* **4**, https://doi.org/10.1016/j.xops.2024.100478 (2024).
93. Gallardo, M. et al. Machine learning can predict anti–VEGF treatment demand in a treat-and-extend regimen for patients with neovascular AMD, DME, and RVO associated macular edema. *Ophthalmol. Retin.* **5**, 604–624 (2021).
94. Zhao, X. et al. Optical coherence tomography-based short-term effect prediction of anti-vascular endothelial growth factor treatment in neovascular age-related macular degeneration using sensitive structure guided network. *Graefes Arch. Clin. Exp. Ophthalmol.* **259**, 3261–3269 (2021).
95. Lee, H., Kim, S., Kim, M. A., Chung, H. & Kim, H. C. Post-treatment prediction of optical coherence tomography using a conditional generative adversarial network in age-related macular degeneration. *Retina* **41**, 572–580 (2021).
96. Schmetterer, L. et al. Endpoints for clinical trials in ophthalmology. *Prog. Retin. Eye Res.* **97**, 101160 (2023).
97. Sun, M. T. et al. Structural and metabolic imaging after short-term use of the balance goggles system in glaucoma patients: a pilot study. *J. Glaucoma* **31**, 634–638 (2022).
98. Levin, L. A., Patrick, C., Choudry, N. B., Sharif, N. A. & Goldberg, J. L. Neuroprotection in neurodegenerations of the brain and eye: lessons from the past and directions for the future. *Front. Neurol.* **13**, 964197 (2022).
99. Wareham, L. K. et al. Solving neurodegeneration: common mechanisms and strategies for new treatments. *Mol. Neurodegener.* **17**, 23 (2022).
100. Williamson, D. J. et al. Artificial intelligence to facilitate clinical trial recruitment in age-related macular degeneration. *Ophthalmol. Sci.* **4**, 100566 (2024).
101. Vayena, E., Blasimme, A. & Sugarman, J. Decentralised clinical trials: ethical opportunities and challenges. *Lancet Digital Health* **5**, e390–e394 (2023).
102. Teo, Z. L. et al. Federated machine learning in healthcare: a systematic review on clinical applications and technical architecture. *Cell Rep. Med.* **5**, https://doi.org/10.1016/j.xcrm.2024.101419 (2024).
103. Pallmann, P. et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med.* **16**, 29 (2018).
104. Huckvale, K. et al. Protocol for a bandit-based response adaptive trial to evaluate the effectiveness of brief self-guided digital interventions for reducing psychological distress in university students: the Vibe Up study. *BMJ Open* **13**, e066249 (2023).
105. Vidovszky, A. A. et al. Increasing acceptance of AI-generated digital twins through clinical trial applications. *Clin. Transl. Sci.* **17**, e13897 (2024).
106. Bordukova, M., Makarov, N., Rodriguez-Esteban, R., Schmich, F. & Menden, M. P. Generative artificial intelligence empowers digital twins in drug discovery and clinical trials. *Expert Opin. Drug Discov.* **19**, 33–42 (2024).
107. Visioli, G. et al. Proliferative vitreoretinopathy in retinal detachment: perspectives on building a digital twin model using nintedanib. *Int. J. Mol. Sci.* **25**, 11074 (2024).
108. Iliuță, M.-E. et al. Digital twin models for personalised and predictive medicine in ophthalmology. *Technologies* **12**, 55 (2024).
109. Li, F. et al. Development and clinical deployment of a smartphone-based visual field deep learning system for glaucoma detection. *npj Digital Med.* **3**, 123 (2020).
110. Chen, W. et al. Early detection of visual impairment in young children using a smartphone-based deep learning system. *Nat. Med.* **29**, 493–503 (2023).
111. Li, J. et al. Integrated image-based deep learning and language models for primary diabetes care. *Nat. Med.* https://doi.org/10.1038/s41591-024-03139-8 (2024).
112. Zong, N. et al. Computational drug repurposing based on electronic health records: a scoping review. *npj Digital Med.* **5**, 77 (2022).
113. Liu, R., Wei, L. & Zhang, P. A deep learning framework for drug repurposing via emulating clinical trials on real-world patient data. *Nat. Mach. Intell.* **3**, 68–75 (2021).
114. Beck, B. R., Shin, B., Choi, Y., Park, S. & Kang, K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. *Comput. Struct. Biotechnol. J.* **18**, 784–790 (2020).
115. Zhou, Y., Wang, F., Tang, J., Nussinov, R. & Cheng, F. Artificial intelligence in COVID-19 drug repurposing. *Lancet Digital Health* **2**, e667–e676 (2020).
116. Ting, D. S. J., Tan, T. F. & Ting, D. S. W. ChatGPT in ophthalmology: the dawn of a new era?. *Eye***38**, 4–7 (2024).
117. Thirunavukarasu, A. J. et al. Large language models approach expert-level clinical knowledge and reasoning in ophthalmology: a head-to-head cross-sectional study. *PLoS Digit. Health* **3**, e0000341 (2024).
118. Yan, C. et al. Leveraging generative AI to prioritize drug repurposing candidates for Alzheimer's disease with real-world clinical validation. *npj Digital Med.* **7**, 46 (2024).
119. Ouyang, B. et al. AI-powered omics-based drug pair discovery for pyroptosis therapy targeting triple-negative breast cancer. *Nat. Commun.* **15**, 7560 (2024).
120. Katwaroo, A. R., Adesh, V. S., Lowtan, A. & Umakanthan, S. The diagnostic, therapeutic, and ethical impact of artificial intelligence in modern medicine. *Postgrad. Med. J.* **100**, 289–296 (2023).
121. Narmadha, K. & Varalakshmi, P. Federated Learning in Healthcare: a privacy preserving approach. *Stud. Health Technol. Inf.* **294**, 194–198 (2022).
122. U.S. Food & Drug Administration. Artificial Intelligence in Software as a Medical Device (SaMD). FDA (published 25 March 2025; accessed 20 August 2025).
123. Warraich, H. J., Tazbaz, T. & Califf, R. M. FDA perspective on the regulation of artificial intelligence in health care and biomedicine. *JAMA* **333**, 241–247 (2025).
124. Mirakhori, F. & Niazi, S. K. Harnessing the AI/ML in drug and biological products discovery and development: the regulatory perspective. *Pharmaceuticals* **18**, 47 (2025).
125. Hutson, M. AI for drug discovery is booming, but who owns the patents?. *Nat. Biotechnol.* **41**, 1494–1496 (2023).
126. Krumplitsch, S. Generative AI, drug discovery, and US patent law. https://www.dlapiper.com/en-cl/insights/publications/synthesis/2024/generative-ai-drug-discovery-and-us-patent-law (2024).
127. School, C. L. 35 U.S. Code § 112—Specification. https://www.law.cornell.edu/uscode/text/35/112 (2024).
128. Keskinbora, K. H. Medical ethics considerations on artificial intelligence. *J. Clin. Neurosci.* **64**, 277–282 (2019).
129. Ong, Z. Z. et al. Diagnostic performance of deep learning for infectious keratitis: a systematic review and meta-analysis. *EClinicalMedicine* **77**, 102887 (2024).
130. Inglada Galiana, L., Corral Gudino, L. & Miramontes González, P. Ethics and artificial intelligence. *Rev. Clín. Esp.***224**, 178–186 (2024).

131. Vasey, B. et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. *Nat. Med.* **28**, 924–933 (2022).
132. Liu, X. et al. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. *Nat. Med.* **26**, 1364–1374 (2020).
133. Cruz Rivera, S. et al. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. *Nat. Med.* **26**, 1351–1363 (2020).
134. Gangwal, A., Ansari, A., Ahmad, I., Azad, A. K. & Wan Sulaiman, W. M. A. Current strategies to address data scarcity in artificial intelligence-based drug discovery: a comprehensive review. *Comput. Biol. Med.* **179**, 108734 (2024).
135. Macedo, B., Ribeiro Vaz, I. & Taveira Gomes, T. MedGAN: optimized generative adversarial network with graph convolutional networks for novel molecule design. *Sci. Rep.* **14**, 1212 (2024).
136. Tiwari, P. C., Pal, R., Chaudhary, M. J. & Nath, R. Artificial intelligence revolutionizing drug development: exploring opportunities and challenges. *Drug Dev. Res.* **84**, 1652–1663 (2023).
137. Blanco-González, A. et al. The role of AI in drug discovery: challenges, opportunities, and strategies. *Pharmaceuticals* **16**, 891 (2023).
138. Jalali, R., Nogueira-Rodrigues, A., Das, A., Sirohi, B. & Panda, P. K. Drug development in low- and middle-income countries: opportunity or exploitation? *Am. Soc. Clin. Oncol. Educ. Book* 3–10 (2022).
139. Ibrahim, H. et al. Reporting guidelines for clinical trials of artificial intelligence interventions: the SPIRIT-AI and CONSORT-AI guidelines. *Trials* **22**, 11 (2021).
140. Sands, B. E. et al. Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis. *N. Engl. J. Med.* **391**, 1119–1129 (2024).
141. Li, Y. et al. Abstract 502: ISM3091, a novel selective USP1 inhibitor as a targeted anticancer therapy. *Cancer Res.* **83**, 502–502 (2023).
142. Insilico. *A Small Molecule KAT6 Inhibitor as a Potential Treatment of ER+ HER2- Breast Cancer (Entering IND)*. https://insilico.com/pipeline_target_kat6 (2024).
143. Ren, F. et al. A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models. *Nat. Biotechnol.* **43**, 63–75 (2025).
144. Booq, R. Y., Tawfik, E. A., Alfassam, H. A., Alfahad, A. J. & Alyamani, E. J. Assessment of the antibacterial efficacy of halicin against pathogenic bacteria. *Antibiotics* **10**, https://doi.org/10.3390/antibiotics10121480 (2021).
145. Treat, J. et al. P2.12-07 phase II trial of LP-300 + pemetrexed/carboplatin in patients who never smoked with lung adenocarcinoma after TKI progression. *J. Thorac. Oncol.* **18**, S365 (2023).
146. Kulkarni, A. et al. LP-184, a novel acylfulvene molecule, exhibits anticancer activity against diverse solid tumors with homologous recombination deficiency. *Cancer Res. Commun.* **4**, 1199–1210 (2024).
147. Zhou, J. et al. LP-284, a small molecule acylfulvene, exerts potent antitumor activity in preclinical non-Hodgkin's lymphoma models and in cells deficient in DNA damage repair. *Oncotarget* **14**, 597–611 (2023).
148. Schmidt-Erfurth, U. et al. Therapeutic response in the HAWK and HARRIER trials using deep learning in retinal fluid volume and compartment analysis. *Eye* **37**, 1160–1169 (2023).
149. Fu, D. J. et al. Deep-learning automated quantification of longitudinal OCT scans demonstrates reduced RPE loss rate, preservation of intact macular area and predictive value of isolated photoreceptor degeneration in geographic atrophy patients receiving C3 inhibition treatment. *Br. J. Ophthalmol.* **108**, 536–545 (2024).
150. Vogl, W.-D. et al. Predicting topographic disease progression and treatment response of pegcetacoplan in geographic atrophy quantified by deep learning. *Ophthalmol. Retin.* **7**, 4–13 (2023).
151. Roberts, P. K. et al. Quantification of fluid resolution and visual acuity gain in patients with diabetic macular edema using deep learning: a post hoc analysis of a randomized clinical trial. *JAMA Ophthalmol.* **138**, 945–953 (2020).
152. Schmidt-Erfurth, U. et al. Disease activity and therapeutic response to pegcetacoplan for geographic atrophy identified by deep learning-based analysis of OCT. *Ophthalmology* https://doi.org/10.1016/j.ophtha.2024.08.017 (2024).
153. Mulyukov, Z. et al. Artificial intelligence-based disease activity monitoring to personalized neovascular age-related macular degeneration treatment: a feasibility study. *Ophthalmol. Sci.* **4**, 100565 (2024).
154. Chandra, R. S. & Ying, G. S. Predicting visual acuity responses to anti-VEGF treatment in the comparison of age-related macular degeneration treatments trials using machine learning. *Ophthalmol. Retin.* **8**, 419–430 (2024).
155. Kikuchi, Y. et al. Machine learning to predict faricimab treatment outcome in neovascular age-related macular degeneration. *Ophthalmol. Sci.* **4**, https://doi.org/10.1016/j.xops.2023.100385 (2024).
156. Maunz, A. et al. Machine learning to predict response to ranibizumab in neovascular age-related macular degeneration. *Ophthalmol. Sci.* **3**, 100319 (2023).
157. Bogunović, H. et al. Prediction of anti-VEGF treatment requirements in neovascular AMD using a machine learning approach. *Invest. Ophthalmol. Vis. Sci.* **58**, 3240–3248 (2017).
158. Chandra, R. S. & Ying, G. S. Evaluation of multiple machine learning models for predicting number of anti-VEGF injections in the comparison of AMD treatment trials (CATT). *Transl. Vis. Sci. Technol.* **12**, 18 (2023).

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Author contributions

H.C., D.S.J.T., and D.S.W.T. conceptualized the paper. H.C., J.W., and C.Q. wrote the main manuscript text and prepared Figs. 1–4 and Tables 1–3. J.G., V.M., T.Y.W., J.M., D.S.W.T., and D.S.J.T. edited all revisions of the manuscript. All authors approved the final manuscript.

Competing interests

D.S.W.T. holds a patent on a deep learning system for the detection of retinal diseases (10201706186V) and a computer-implemented method for training an image classifier using weakly annotated training data (10201901083Y) and stocks at EyRIS, Singapore and aISIGHT. The other authors declare no conflicts of interest.

Additional information

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