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PERSPECTIVE

When artificial intelligence (AI) meets organoids and organs-on-chips (OoCs): Game-changer for drug discovery and development?

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Research and development (R & D) of new drugs is a core engine driving medical progress and plays a crucial role in shaping human health and well-being. Challenges to the conventional drug discovery and development (DDD) pipeline include high cost, long duration, and unsatisfactorily high drug attrition rates. Recently, artificial intelligence (AI) and organoids/organs-on-chips (OoCs) have emerged as revolutionary toolboxes for potentially transforming therapeutic development. By analyzing large-scale datasets and complicated biological networks, AI promises to significantly impact modern drug innovation. Organoids/OoCs are emerging *in vitro* biological models that mimic the essential characteristics of human organs and tissues, offering potentially unparalleled physiological relevance and predictive power for *in vitro* disease modeling and pharmaceutical development. Over the past few years, several AI- or/and organoids/OoCs-discovered drugs have entered clinical trials, signaling the dawn of a new era of DDD. Notably, utilizing AI and organoids/OoCs simultaneously combines the best of both worlds and represents an innovative strategy to potentially expedite DDD. In this Perspective, we briefly introduce the general concepts of AI and organoids/OoCs, explore their state-of-the-art applications in DDD, and discuss why and how their synergistic impacts can revolutionize the R & D of new drugs. We also address current limitations and propose potential solutions to propel this innovative approach forward.

ORGANOIDS AND OoCs: EMERGING DISEASE MODELING MODALITIES FOR MEDICINAL DEVELOPMENT

While drug candidates undergo rigorous testing and extensive optimization during preclinical stages, the average failure rate for over 21,143 compounds in clinical trials from January 1, 2000 to October 31, 2015 reached 86.2%.[1] These unsatisfactory results can be partially attributed to the low predictive power of animal models, such as mice, rats, pigs, goats, and nonhuman primates, due to their many anatomical, physiological, and genetic differences from human patients. As humanized models, organoids and OoCs are revolutionizing biomedical research by more accurately and efficiently recapitulating human pathophysiology for disease studies and drug testing.[2,3]

Organoids are *in vitro* miniature organ-like constructs typically derived from the self-assembly of pluripotent/adult stem cells or tissue biopsies, e.g., tumors, in a three-dimensional (3D) culture.[3] Organoids can closely mimic the key functional, structural, and biological complexity, i.e., cellular heterogeneity and hierarchy, of their native counterparts, making them valuable and versatile platforms for studying organ development, disease progression, and drug response.[3] Organoids have been employed to model various organ/tissue types, e.g., brain, liver, intestine, etc., as well as a wide range of diseases, including genetic disorders, infectious diseases, and rare diseases that may be challenging, if not impossible, for animal-based modeling.[3] Moreover, patient-specific organoids open the door to personalized drug safety and efficacy testing. OoCs are microphysiological systems that offer a dynamic, precisely modulated microenvironment conducive to the formation of microtissues possessing the essential functional features of native organs/tissues.[2] Established with transdisciplinary technologies, OoCs are capable of accommodating multiple cell types and replicating interstitial/blood flow, thereby emulating multi-organ interactions and drug metabolism.[2] OoCs are particularly useful for toxicity testing and are emerging tools to address the insufficient predictive power of animal testing. In summary, organoids/OoCs are human cell-based, advanced *in vitro* models with high (patho)physiological complexity and clinical relevance that can facilitate disease modeling and fuel the development of safer and more effective drugs.

Organoids and OoCs each offer unique advantages and face specific limitations in disease-specific drug discovery. Organoids excel in cellular fidelity, ease of generation and implementation, and integration with next-generation data analyses but mostly lack vascularization and standardization, while OoCs provide precise microenvironmental control and enable dynamic multi-organ interactions and *in situ* monitoring but are limited by technical complexity, drug interactions with chip materials, and higher costs.[2,3] Integrating both models can lead to a more comprehensive approach to drug discovery, combining their strengths and addressing their weaknesses. Organoids-on-a-chip systems merge the complex 3D architecture, cellular diversity, and spatial organization of organoids with the precise microenvironmental control and real-time monitoring capabilities of OoC platforms, providing enhanced physiological relevance and reproducibility, thereby advancing drug development and disease research.[4]

AI-POWERED DRUG DISCOVERY AND DEVELOPMENT: A COMING WAVE FOR PARADIGM SHIFT

In today's data-rich landscape, datasets of high-dimensional multiomics such as genomics, epigenomics, transcriptomics (including single-cell profiling), proteomics, and metabolomics, high-content imaging, and population-scale collation of electronic healthcare records are now commonplace. Confronted with vast, diverse, and complex information, traditional data processing methods lack scalability and flexibility to identify indiscernible patterns and insights. AI excels in data analysis by employing machine learning (ML) and deep learning (DL) algorithms to sift through the sheer volume of datasets with unprecedented speed and accuracy.[5,6] AI can be leveraged to benefit several vital stages in the realm of therapeutic development (e.g., target identification and validation, drug screening and lead optimization, preclinical tests, clinical trials, and post-approval surveillance), enabling a paradigm shift from a conventional time-consuming, costly, and risk-laden process to a more efficient and reliable journey.[5]

The most important feature of AI is that it can provide data-driven insights that can be applied in various aspects of the drug discovery pipeline, including biomarker/target identification, drug-target interaction prediction, phar-

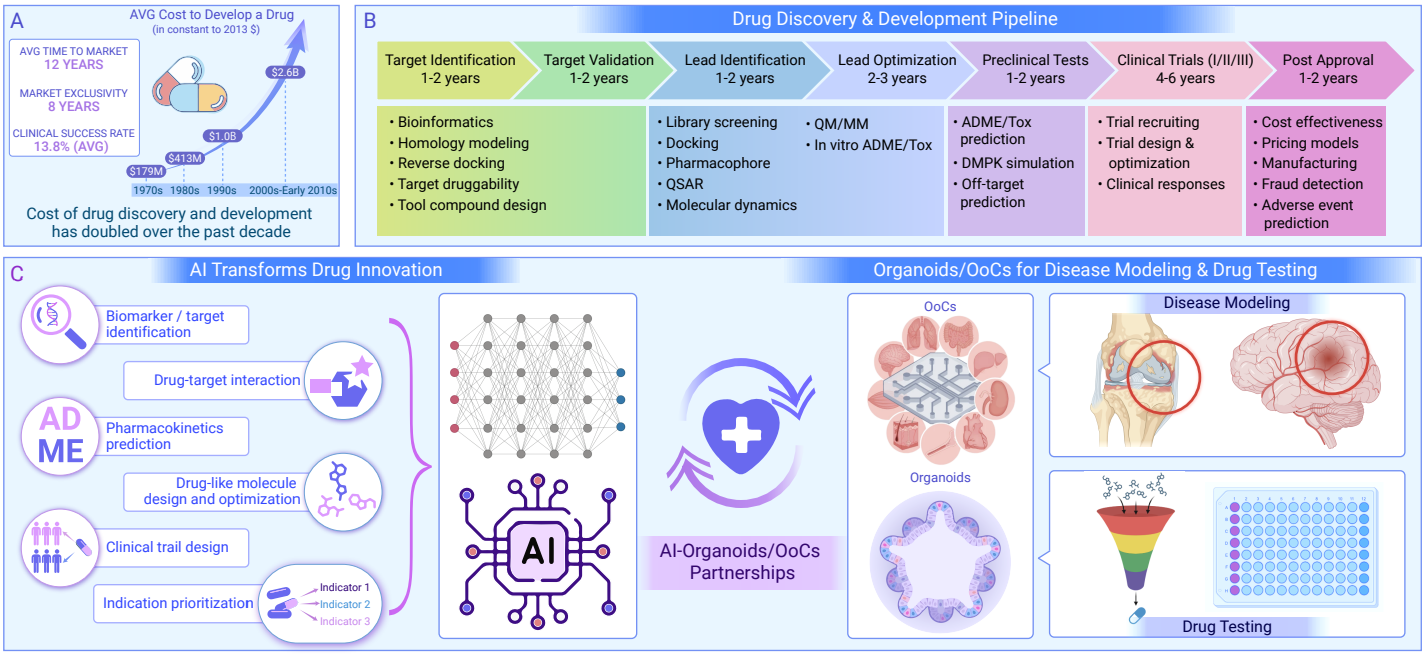

Figure 1. AI-organoids/OoCs partnerships aim to pioneer a new drug innovation era (A) The conventional drug discovery and development (DDD) pathway is widely recognized to be a time-consuming, expensive, and risk-laden process that typically requires around 12 years and > US$ 2.6 billion from the initial drug discovery to market. (B) Each key step in the DDD pipeline. (C) The seamless integration of AI and organoids/OoCs has the potential to redefine the landscape of drug innovation across various stages by leveraging the merits of both technologies. (QSAR: quantitative structure-activity relationship; QM/MM: quantum mechanics/molecular mechanics; ADME/Tox: absorption, distribution, metabolism, excretion/toxicology; DMPK: drug metabolism and pharmacokinetics.)

macokinetics prediction, drug-like molecule design, chemical structure optimization, clinical trial design, and indication prioritization and drug repurposing. Specifically, AI enables researchers to efficiently identify highly promising targets, a process that previously took years but can now be accomplished in a matter of days or months. For instance, BenevolentAI, a leading company in AI-driven drug discovery, utilized its proprietary AI platform to identify baricitinib as a potential treatment for COVID-19 during the early stages of the pandemic. The AI system analyzed vast datasets, including biological pathways, disease mechanisms, and available drug libraries, to suggest baricitinib as a promising candidate due to its dual role in inhibiting viral entry and modulating the immune response.[7] This accelerated the drug repurposing process, moving baricitinib to clinical trials in record time, showcasing the transformative role that AI can play in identifying viable therapeutic targets efficiently. In lead discovery, AI can predict the therapeutic efficacy of millions of compounds and optimize their chemical structures, streamlining the drug candidate selection process via automating high-throughput screening (HTS), virtual screening, and *de novo* drug design. During this process, generative AI, a subset of AI, is particularly noteworthy for its ability to 'imagine' the plethora of unchartered molecular structures that fit specific pharmacological profiles, thereby expanding the boundaries of explored chemical space. To enhance the precision and effectiveness of therapeutic interventions, AI also aids in predicting patient responses, personalizing treatment plans, and simulating clinical trial outcomes. With continuous evolution, AI is poised to become an invaluable and indispensable tool in our quest for new and efficacious therapeutics, heralding a new wave of pharmaceutical innovation, especially for complex and challenging diseases.

INTEGRATION OF AI AND ORGANOIDS/OoCs: HOW TO REALIZE 1+1≫2

To date, several AI-driven drug candidates have advanced into clinical trials. For example, Exscientia's drug EXS-21546 is currently in phase Ib/II trials for patients with solid tumors characterized by high adenosine signatures.[8] Insilico Medicine's first-in-class drug, INS018_055, advanced from initial discovery to preclinical testing in just 18 months, which was significantly faster than typically required by traditional drug discovery methods.[9] In June 2024, Insilico Medicine reported the completion of patient enrollment in its phase IIa study in China investigating INS018_055 for idiopathic pulmonary fibrosis.[10] Meanwhile, some organoids/OoCs-tested drugs (e.g., Petosemtamab, TNT005, and HRS-1893) have been approved by regulatory authorities to enter clinical trials based on the efficacy and safety data from organoid/OoC models. The above-mentioned examples underscore the growing impact and acceptance of AI and organoids/OoCs in DDD, especially in preclinical studies. It is envisioned that AI-organoids/OoCs partnerships will result in a powerful synergy that can be fully unleashed and leveraged to facilitate DDD (Figure 1). This synergy enhances efficiency and accuracy and reduces time, costs, and ethical concerns (by using fewer animal models), propelling drug discovery toward improved clinical outcomes. Nevertheless, such AI-organoids/OoCs integration for the R & D of new drugs is a multifaceted endeavor that requires a strategic approach to unlock the full potential of both components.

Above all, data acquisition and management are two pivotal aspects of attaining efficient and effective AI-organoids/OoCs integration. The first step is establishing robust protocols for data collection from organoids/OoCs.[5] Organoids/OoCs-based disease modeling and drug testing can produce high-quality images (e.g., by immunofluorescence imaging), real-time biosensor-generated data (e.g., biochemical or biophysical parameters), and detailed molecular profiling.[5] AI systems require large datasets for training, so it is crucial to have standardized, high-volume data collection methods. Developing advanced ML algorithms to decode complex organoid/OoC data is also essential for predicting drug efficacy or side effects based on organoid/OoC responses.[5] DL, particularly convolutional neural networks (CNNs), can be utilized for organoids/OoCs image analysis to track alterations over time, detect anomalies, and even predict cellular responses to different compounds.[5] Besides, AI and organoids/OoCs empower automated HTS in drug discovery.[5] Researchers can leverage AI tools to automatically test thousands of compounds on organoid/OoC platforms, markedly expediting the drug identification and optimization process. Combining AI-based predictive modeling with data derived from organoids/OoCs-based disease modeling makes it possible to forecast drug behaviors in a more human-relevant context before clinical trials.[5] Additionally, AI can help standardize wet-lab experiments involving organoids/OoCs and enhance reproducibility, which has been challenging to achieve because of the wide range of variables involved in relevant processes. For instance, ML can assist in fine-tuning the experimental conditions across different labs and over time. AI, such as generative models, reinforcement learning, and evolutionary algorithms, can also be employed to design and optimize microfluidic devices, e.g., macro-/micro-structure, flow dynamics, mechanical stimuli, chemical concentration gradient, tissue-tissue interface, and cell-cell interaction, and the composition and structure of novel hydrogel biomaterials for culturing organoids. AI-

organoids/OoC partnerships can significantly contribute to the development of precision medicine by facilitating patient classification, predicting patient-specific drug responses, elucidating disease mechanisms for different patient subgroups, and supporting clinicians' decision-making with ML algorithms. Last but not least, joint efforts from academia, industry, and government, are urgently required to address the considerations of ethical implications and regulatory compliance, including data privacy, algorithmic transparency, and informed consent, as well as the ethical use of AI predictions and human cell-derived organoids/OoCs.[5] Of particular note is that the involvement of government and regulatory bodies is crucial for providing funding support, regulatory oversight, guidelines on standardization, and ethical and legal framework as well as facilitating collaborations between academia, industry, and the public sector to the successful clinical translation of discoveries in drug development and precision medicine.

CURRENT DILEMMA

Currently, integrating AI with organoids/OoCs in the R&D of drugs, especially first-in-class drugs, still faces several challenges. First, the sheer amount of organoid/OoC data can be highly complicated, posing difficulties for AI algorithms in terms of processing and analysis.[5] Integrating heterogeneous data types (e.g., imaging, genomic, proteomic, and functional data) into a cohesive framework for AI analysis is highly complex and requires sophisticated algorithms.[5] AI models may also struggle with generalizing data in organoid/OoC studies which lack standardized protocols and experimental conditions across different labs with concerns of reproducibility and standardization.[2,3] Apart from these challenges, data quality, AI model interpretability, and standardization must be addressed to realize the widespread implementation of AI. Additionally, we should also address the use of AI in the assessment of specific metrics, such as images, leading to the improvement of diagnostic information, the reduction of operator errors when reading images, and the improvement of image analysis (such as classification, localization, regression, and segmentation).

Organoids/OoCs, while considered more human (patho)physiology-relevant than animal testing, still lack structural, compositional, and functional complexity of native tissues/organs, and thus simplify the intricate cellular interactions within human tissues/organs.[2,3] To improve the predictive power of organoid/OoC models, one could consider incorporating complexity enhancement, functional assays (e.g., drug metabolism and elimination), physiological parameters (e.g., electrical signals and contractility), long-term cultures, patient-specific models of organoids/OoCs (e.g., patient-derived tumor organoids), and integration with AI. Meanwhile, ensuring the scalability of organoids/OoCs-based HTS allows efficient testing with minimal sample consumption. However, challenges frequently arise in balancing throughput optimization and the maintenance of disease relevance and robustness, as well as in managing data efficiently as the screening scales up.[2,3] Additionally, using AI-powered organoid/OoC platforms in drug discovery may raise concerns over ethical and regulatory non-compliance in the following aspects.[2,3,5] AI, not humans, will make decisions on diagnosis and treatment options. Enhancing algorithmic transparency and interpretability is critical to ensure that DL models, often perceived as 'black boxes', can be trusted and validated by researchers and regulators. Besides, concerns persist regarding cell/data sources, privacy, informed consent, and the responsible use of AI and organoids/OoCs. Moreover, the lack of essential infrastructure (e.g., supercomputing facilities), technical expertise, and financial support in AI and organoid/OoC platforms may hinder the widespread adoption of AI-powered organoid/OoC platforms in pharmaceutical development. Lastly, integrating distinct organoid/OoC data or data patterns to yield a cohesive understanding of drug effects is a complex task that necessitates the development of advanced AI tools.

CONCLUSION

When AI meets organoids/OoCs, a game-changer emerges to reshape the DDD pipeline. By harnessing AI's robust analytical capacities coupled with potential predictive capabilities as well as the (patho)physiological relevance of organoids/OoCs-based *in vitro* disease modeling, a more efficient, effective, and human-centric strategy can be established. The seamless integration of AI and organoids/OoCs has the potential to redefine the landscape of drug innovation across various stages by leveraging the merits of both technologies. This integration may offer a new avenue for translating novel, groundbreaking findings from AI-assisted organoids/OoCs-based DDD into clinical practice. While several AI-discovered drugs and organoids/OoCs-evaluated drugs have progressed to clinical trials, none have yet received regulatory approval, underscoring the need for careful navigation of the technical, ethical, and regulatory challenges. It is envisioned that through continuous refinement and interdisciplinary efforts, AI-potentiated organoids/OoCs-based DDD strategy will bring highly precise, targeted, and patient-specific therapeutics in the near future.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.