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Crossing Disease Boundaries: How AI Drives Rare Disease Drug Discovery

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Abstract This article explores the challenges and prospects of using AI to advance rare disease drug discovery. With its complex genetic basis, rare diseases require precise diagnosis and personalized treatment approaches, necessitating further development of sequencing technologies, bioinformatics tools, and data analysis algorithms. Data collection and sharing pose challenges due to the limited number of rare disease patients. Collaboration and favorable policy environments are equally crucial to drive rare disease drug discovery, as international collaborative networks and supportive policies facilitate data and resource sharing and provide research and market support. Future trends include personalized medicine, application of AI technologies, and exploration of drug repurposing and combination therapies, which will drive innovation and progress in rare disease drug discovery.

Keywords Rare disease; Artificial intelligence (AI); Technological challenges; Data sharing

In the field of medicine, rare diseases have always been a thorny issue. Although their incidence rate in the total population is relatively low, rare diseases have brought huge social and medical challenges to patients and their families. Li et al. (2018) found that these challenges stem not only from the complexity and diversity of diseases, but also from the various difficulties in developing rare disease drugs. With the rapid development of artificial intelligence (AI) technology, new hope has been seen to overcome these challenges.

Although the incidence rate of rare diseases is low, there are many kinds of rare diseases, covering a wide range of fields from genetic diseases to complex syndromes. These diseases are often accompanied by unique pathological mechanisms and clinical manifestations, making diagnosis and treatment exceptionally difficult. For many rare disease patients, the lack of effective treatment drugs and plans is the biggest challenge they face. In addition, due to the relatively small number of rare disease patients, the cost and resource investment of drug development are also greatly limited.

At the same time, the rise of AI technology has brought revolutionary changes to the discovery of rare disease drugs (Chakravarty et al., 2021). AI has powerful data processing and analysis capabilities, which can extract valuable information from massive biomedical data and provide new ideas and methods for drug development. In the field of medical and health, AI has been widely applied in image recognition, disease prediction, personalized treatment, and other aspects, demonstrating a huge range of applications and potential.

This study aims to explore how AI promotes the process and mechanism of rare disease drug discovery. Through in-depth research and analysis, it is hoped that the key role of AI technology in the development of rare disease drugs can be revealed, providing new ideas and methods for future drug development. At the same time, it is also hoped that this study will attract more attention and investment in the development of rare disease drugs, bringing more treatment options and hope to rare disease patients (Smith, 2022). This study not only has important scientific value, but also has profound social significance. I hope to contribute to the development of rare disease drug discovery and bring better treatment prospects to patients with rare diseases through efforts.

1 The Challenge of Discovering Rare Disease Drugs

1.1 Research and development costs and resource constraints

The high cost of developing rare disease drugs is mainly due to the significant investment in clinical trials, drug production, and market promotion involved in the research and development process (Groft et al., 2021). The

clinical trial cost of rare disease drugs is 50% of non rare disease drugs before deducting tax deductions; The median cost of conducting global clinical trials for non rare disease drugs is approximately 33.4 million US dollars. Therefore, if considering clinical trial costs and tax deductions, the median clinical trial cost of rare disease drugs is approximately 8.35 million US dollars (Koreiweian, 2018, http://www.yyjjb.com.cn/). For many pharmaceutical companies, the imbalance between investment and return on investment in rare disease drug development makes it difficult for them to bear this economic pressure.

In the field of drug discovery and development for rare genetic diseases, Sun et al. (2017) conducted groundbreaking work aimed at overcoming significant challenges in this field. The research team pointed out that although rare diseases have a significant impact on patients, there is a significant gap between basic research and clinical intervention for these diseases. They emphasize that there are already opportunities to accelerate the development of rare disease drugs, and disease foundations and research centers worldwide are focusing on better understanding these rare diseases (Polizzi et al., 2014).

According to Tang et al. (2022), the distribution of anti-tumor drug development is not balanced among different types of tumors. For rare tumors with low incidence rate, the number of patients is small and it is difficult to carry out clinical trials, leading to relatively low research and development enthusiasm in this field. But the treatment needs of patients also bring potential opportunities for pharmaceutical companies. The development of basic research and the discovery of new tumor molecular subtypes have made "Rare tumors" a dynamic concept, and its scope may gradually expand with the precision of treatment.

Yang et al. (2023) summarized the incentive policies for the development of rare disease treatment drugs from 2015 to present. Through literature review and public information, they sorted out the information of drugs approved for the treatment of rare diseases in the first batch of rare disease catalogs from 2018 to 2023, and analyzed the current status of rare disease drug development in China. It is recommended to regularly update the list of rare diseases, strengthen the protection of the rights and interests of rare disease drug developers, encourage the replication of high-quality rare disease drugs, and promote the innovative development of the rare disease drug research and development industry to meet the medication needs of rare disease patients.

1.2 The complexity of scientific research

The scientific complexity of drug development for rare diseases mainly stems from the complexity and heterogeneity of the disease itself (Liu et al., 2022). Many rare diseases are caused by genetic mutations, environmental factors, or the interaction of multiple factors, which requires researchers to deeply explore the molecular mechanisms, pathophysiological processes, and progression pathways of diseases. These diseases often have unique pathogenesis and pathological processes, which make traditional drug development methods difficult to be effective.

Boycott and Ardigò (2017) provided an in-depth analysis of current challenges and explored ways to overcome them. They pointed out that although significant progress has been made in gene discovery in recent years, translating these findings into treatment plans still poses challenges. This is mainly due to the difficulty in diagnosing rare diseases and the lack of specific treatment methods for these diseases.

In June 2021, Risdiplam powder for oral solution was approved for marketing in China as a Class 1 chemical drug for the treatment of spinal muscular atrophy patients aged 2 months and above. In the early stage of clinical research and development, the applicant actively communicates with regulatory authorities, adopts an international multicenter trial design, and tries to include Chinese patients in the study as much as possible. Under the same experimental design and implementation system, the applicant obtains full chain trial data of Chinese patients, including pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety (Chen et al., 2022).

1.3 Research and market factors

The development of rare disease drugs still needs to face strict regulatory approvals and complex market environments. Due to the particularity and complexity of rare disease drugs, their development process requires

strict regulatory approval to ensure the safety and efficacy of the drugs (Qiu et al., 2020). This includes the design and implementation of clinical trials, as well as the evaluation of drug safety and efficacy. However, strict regulatory approval processes may lead to longer drug development cycles and increased research and development costs. In addition, regulatory agencies may have stricter and more cautious approval standards for rare disease drugs to ensure their safety and efficacy.

In 2018, Kempf et al. delved into the specific challenges of conducting clinical trials for rare diseases, proposing to expand the patient base through international cooperation and multicenter trials, while utilizing patient registration systems and social media to improve recruitment efficiency. Through the challenge of developing rare disease drugs, the research team collaborates with international partners to conduct clinical trials. Recruiting patients in multiple countries simultaneously not only expands the patient base, but also accelerates the process of clinical trials (Kempf et al., 2018).

Li et al. (2018) discovered CRISPR/Cas9 gene editing technology and its application in the field of biomedicine, including its important role in cancer treatment and precision medicine. The therapeutic effect of Keytruda (PD-1 inhibitor) on MSI-H/dMMR cancer was mentioned, as well as the innovative application of CRISPR technology in gene therapy, such as constructing more effective CAR-T cells through gene editing technology and identifying key genes in cancer immunotherapy.

The 2024 Illness challenge foundation survey found that with the promotion of a series of policies in the field of rare disease treatment in China, the number of products developed and launched by Chinese companies, whether it is innovative drugs or generic drugs, is increasing. In 2023, Chinese pharmaceutical companies launched 8 new and generic drugs for rare diseases, except for 2 with dosage form/specification adjustments. It is foreseeable that with the continuous promotion of the rare disease field in China, more Chinese companies will expand into the rare disease field and further promote the listing of drugs in the rare disease field (https://img.frostchina.com/attachment/17091360/nfCpGPwYkbfzchSGz1saSN.pdf).

2 The Role of AI in Drug Discovery

2.1 Accelerate the identification of drug targets

Artificial intelligence (AI) plays an important role in drug discovery, one of which is to accelerate the identification process of drug targets. Traditionally, the identification of drug targets is a complex and time-consuming process that requires extensive experimentation and data analysis (Tang et al., 2020). However, AI utilizes its powerful data processing and pattern recognition capabilities to efficiently analyze massive amounts of biological, genetic, and clinical data, identifying potential drug targets from them.

Kubota et al. (2019) reviewed the application of chemical proteomics methods in target deconvolution in phenotypic drug discovery, discussing strategies such as affinity purification based on compound immobilized beads, photoaffinity labeling (PAL), cell thermal shift analysis (CETSA), and activity-based protein profiling (ABPP).

Visibelli et al. (2023) found that during the treatment process, AAV serves as a carrier, carrying two zinc finger nucleases and a normal IDS gene directly to human liver cells. After reaching the interior of liver cells, zinc finger nuclease is specifically activated within liver cells to recognize, bind, and cleave endogenous albumin gene loci. By utilizing the innate DNA repair mechanism of cells, liver cells can insert genes encoding normal IDS into this site to complete individual cell repair (Figure 1).

2.2 Optimizing the compound screening process

Another important role of artificial intelligence in drug discovery is to optimize the compound screening process. Traditional drug screening typically involves testing a large number of compounds in the laboratory to identify molecules that are active towards the target target (Chakravarty et al., 2021). However, this screening process is time-consuming and laborious, and cannot fully cover all possible compound spaces. AI can accelerate and optimize the process of compound screening through virtual screening and prediction models.

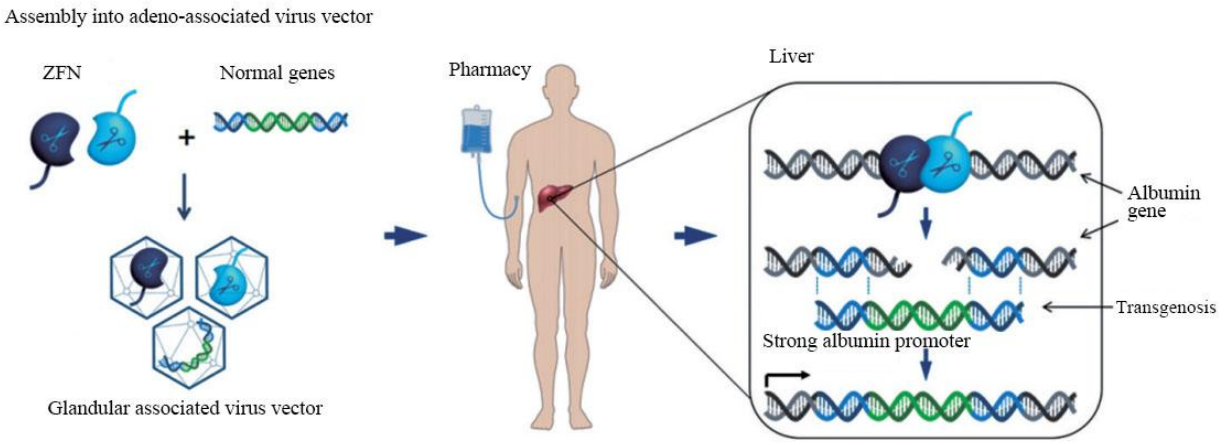

Figure 1 In vivo genome editing of albumin: harnessing the liver's mosthighly expressed locus (Li et al., 2018)

Li et al. (2018) discussed the application of AI in identifying potential drugs and how it can help reduce the failure rate of drug development, potentially improving some of the biggest challenges faced by the pharmaceutical industry, such as high failure rates in clinical trials. Emphasis was placed on the collaboration between the AI based technology platform Atomwise and over 20 research institutions and pharmaceutical companies, showcasing the broad application prospects of AI technology in the pharmaceutical field.

Lim et al. (2016) proposed a fast and accurate method for predicting drug targets, which can explore chemical and protein spaces and their interactions on a large scale, helping to reposition drugs and predict drug side effects.

2.3 Predicting drug efficacy and side effects

Another important role of artificial intelligence in the discovery of rare disease drugs is to predict the effectiveness and side effects of drugs. In the process of drug development, understanding the efficacy and potential side effects of drugs is crucial, and AI can provide accurate and fast predictive models to help researchers better evaluate the efficacy and safety of drugs.

Through machine learning and deep learning algorithms, AI can analyze a large amount of biological data, drug chemical structures, and clinical trial results to establish predictive models for predicting drug efficacy (Visibelli et al., 2023). These models can consider multiple factors, such as the mechanism of action of drugs, molecular interactions, biological pathways, etc., in order to predict the therapeutic effect of drugs on specific diseases.

Walters and Barzilay (2021) reviewed the application of AI in drug discovery, including property prediction, molecular generation, image analysis, and organic synthesis planning, and evaluated the potential and challenges of AI technology in improving drug discovery efficiency. It can help researchers screen and optimize candidates in the early stages of drug development, thereby selecting the most promising drug candidates more targeted.

3 Case Study on AI Driving the Discovery of Rare Disease Drugs

3.1 Success case analysis

In the field of AI driving the discovery of rare disease drugs, some remarkable successful cases have emerged. For example, in 2016, an application called Breathe RM, led by Andres Floto, an outstanding professor of respiratory biology at the University of Cambridge, was changing the way patients with cystic fibrosis (CF) are cared for (Viviani et al., 2016). This innovative technology, through advanced algorithms, can predict in advance when patients will fall ill, up to 10 days in advance. This breakthrough technology will redefine the monitoring methods for CF patients, enabling remote tracking and reducing frequent and time-consuming visits.

The concept of Breathe RM is a comprehensive to-do list that serves as a key tool for remote monitoring of CF patients. By simplifying the collection and prediction of important information required for potential health complications, this application requires users to input daily data. The application seamlessly integrates with handheld spirometers for measuring lung function and nail oximeters for assessing blood oxygen levels. Through

Bluetooth connection, these devices input data into the application. In addition, Breathe RM also integrates data from personal smartwatches, and patients actively contribute to the data pool by self-reported cough frequency and overall health status. This comprehensive approach ensures a comprehensive understanding of the patient's condition (https://www.cryptopolitan.com/ai-powered-app-10-days-cystic-fibrosis/).

3.2 The role of data and algorithms

Behind successful cases, the role of data and algorithms cannot be ignored. In the discovery of rare disease drugs, the accessibility and quality of data are crucial for the application of AI. Large scale genomic data, clinical data, and drug databases provide AI with rich information sources that can reveal the etiology, biological pathways, and drug targets of rare diseases. The selection and optimization of AI algorithms are also key to success. The application of machine learning and deep learning algorithms can process complex biological data, mine hidden patterns and correlations (Zheng et al., 2019). The continuous optimization and iteration of algorithms enable AI models to more accurately predict the efficacy, side effects, and safety of drugs. Therefore, the full utilization of data and algorithms is an important factor in promoting the discovery of rare disease drugs.

The successful case of Breathe RM suggests that this AI driven application may become a broader model for disease management. It can improve the quality of life of patients, reduce unnecessary visits and medical burden. In addition, this technology also provides valuable data resources for researchers to further understand the development and management of cystic fibrosis and other respiratory diseases.

3.3 The value of interdisciplinary cooperation

The discovery of rare disease drugs requires interdisciplinary collaboration, and AI technology provides a platform for collaboration and communication among experts from different fields. The collaboration between biologists, doctors, pharmaceutical chemists, and data scientists can bring together their professional knowledge and skills to address the challenges in rare disease drug discovery (Bendowska and Baum, 2023). As a tool and bridge, AI can integrate data and knowledge from different fields, accelerate information sharing and communication. Through interdisciplinary collaboration, researchers can gain a more comprehensive understanding of the characteristics and mechanisms of rare diseases, and design more effective drug strategies. Interdisciplinary collaboration has important value in promoting the discovery of rare disease drugs, and AI, as a collaborative tool, provides support and assistance for expert collaboration in different fields.

The case studies of AI in promoting the discovery of rare disease drugs have demonstrated its enormous potential. The role of data and algorithms is crucial for successful cases, providing a rich source of information and optimized models. At the same time, interdisciplinary cooperation is also key to promoting the discovery of rare disease drugs. AI, as a collaborative tool, promotes communication and cooperation among experts in different fields. These case studies provide new therapeutic hope for patients with rare diseases and lay the foundation for future research and development.

4 Challenges and Prospects

4.1 Technical and data challenges

In the process of promoting the discovery of rare disease drugs, technology and data are one of the main challenges (Nestler-Parr et al., 2018). Rare diseases often have complex genetic foundations, thus requiring highly accurate molecular diagnosis and personalized treatment methods. However, existing technological tools still have limitations in dealing with this complexity. Further development and improvement are needed in high-throughput sequencing technology, bioinformatics tools, and data analysis algorithms to better understand the genetic mechanisms of rare diseases.

Due to the small number of rare disease patients, data collection and sharing also face challenges. In the process of traditional drug discovery, large-scale sample data is crucial for establishing accurate models and predictions. Groft et al. (2021) found that the limited number of patients with rare diseases makes data collection difficult. It is necessary to establish a global collaborative network to promote data sharing and collaborative research, expand the scale of rare disease datasets, and improve the accuracy of disease prediction and drug discovery.

Despite the challenges in technology and data, significant progress can be expected in the coming years with the rapid development of fields such as artificial intelligence, machine learning, and data science. By integrating multiple technologies and data resources, it is expected to overcome technological and data challenges and bring new breakthroughs to the discovery of rare disease drugs.

4.2 Cooperation and policy environment

Promoting the discovery of rare disease drugs requires establishing a good cooperation and policy environment. Firstly, collaboration is a key factor in promoting research on rare diseases and drug discovery. Due to the limited number of patients with rare diseases, it is difficult for a single institution to obtain sufficient samples and data for research (Groft et al., 2021). Therefore, establishing an international cooperation network, including medical institutions, research institutions, pharmaceutical companies, and patient organizations, is key to promoting the discovery of rare disease drugs. This cooperation can promote data sharing, resource sharing, and knowledge exchange, accelerate research progress and drug development.

The policy environment also plays an important role in promoting the discovery of rare disease drugs, and governments and regulatory agencies need to formulate corresponding policies and regulations to promote the research and marketing of rare disease drugs (Wen et al., 2018). This may include providing research and development funding, optimizing evaluation processes, implementing incentive measures, and reducing market entry barriers. The government should also strengthen the protection of patients with rare diseases, ensuring that they have access to appropriate medical resources and medication treatment.

With the support of cooperation and policy environment, more progress can be expected in the discovery of rare disease drugs. International cooperation will strengthen research capabilities, promote knowledge sharing and technological exchange. Meanwhile, a favorable policy environment will provide more impetus and support for research institutions and pharmaceutical companies to promote the research and marketing of rare disease drugs.

4.3 Future development trends

In the future, the discovery of rare disease drugs will face some key development trends, and personalized healthcare will become an important direction for rare disease drug discovery. With the rapid development of genomics and biotechnology, it is possible to better understand the genetic mechanisms of rare diseases and provide personalized treatment plans for patients. Through gene sequencing and analysis, it is possible to identify mutated genes in patients and develop targeted drugs based on their individual characteristics. Personalized healthcare will bring more precise and effective treatment methods to patients with rare diseases (Miller et al., 2021).

Drug repositioning and drug combination therapy will also become future development trends. Drug repositioning refers to the application of existing drugs to new pathological targets, which can accelerate the drug development process and reduce research and development costs. The drug combination therapy principle utilizes the synergistic effect of multiple drugs to improve treatment effectiveness. These methods have great potential in the discovery of rare disease drugs, expanding the range of treatment options and improving treatment success rates.

The discovery of rare disease drugs in the future will benefit from development trends such as personalized healthcare, artificial intelligence technology, drug repositioning, and combination therapy (Goetz and Schork, 2018). These trends will drive innovation and progress in the treatment of rare diseases, providing patients with better medical choices. With the continuous development of technology and cooperation, there is reason to be confident in the future of rare disease drug discovery.

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