THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
September 2024 Vol.4(9), 3568-3571

Popular Article

Drug Discovery for Parasitic Diseases: Powered by Advanced Technology and Enabled Pharmacology

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https://doi.org/10.5281/zenodo.13768129

Abstract

This article explores the latest breakthroughs in drug discovery for parasitic diseases, highlighting how cutting-edge technologies like artificial intelligence and high-throughput screening are revolutionizing the field. From identifying new drug targets to streamlining clinical trials, these innovations are helping scientists develop more effective treatments faster. Despite these advancements, challenges like drug resistance and limited resources persist, making ongoing research and collaboration essential to combating these widespread diseases and improving global health.

INTRODUCTION

Parasitic diseases, caused by protozoa, helminths, and arthropods, are a significant global health challenge, impacting over one billion people annually and leading to millions of deaths. The development of new treatments has been challenging due to the complexity of parasites and high costs associated with drug discovery. Despite these obstacles, advancements in genomics, proteomics, metabolomics, and nanotechnology are leading to innovative approaches and the development of promising new drugs.

STAGES IN DRUG DISCOVERY AND DRUG REPURPOSING

The drug discovery process for parasitic diseases involves several stages, starting with target identification to find potential drug targets, followed by hit discovery and screening to identify active compounds. These compounds are then optimized for better efficacy and safety, tested in preclinical animal models, and subjected to rigorous clinical trials. Finally, post-marketing surveillance ensures long-term safety and effectiveness. This comprehensive process (de novo) is costly and time-consuming typically taking 13-15 years and $2-3 billion for new drugs. Drug repurposing offers a more efficient alternative by using existing compounds, significantly reducing development time and cost, and involves fewer stages *viz.* selection of a target compound, phase 2 and 3 clinical trials, NDA

application, and post-marketing surveillance, making it a promising approach for accelerating the availability of new treatments.

ADVANCED TECHNOLOGY IN DRUG DISCOVERY:

1. Artificial Intelligence (AI) and Machine Learning (ML)

Artificial Intelligence (AI) and Machine Learning (ML) are transforming drug discovery by analyzing large datasets to uncover patterns, predict biological activities, and optimize drug candidates. ML enhances Quantitative Structure-Activity Relationship (QSAR) analysis, accelerates hit discovery, and enables de novo drug design. Additionally, ML improves target validation through omics data analysis and advances prognostic biomarkers and digital pathology.

2. High-Throughput Screening (HTS) and Automation

High-Throughput Screening (HTS) and automation are crucial for rapidly assessing large compound libraries. For example, HTS of over 2 million compounds led to the identification of potent hits against *Plasmodium falciparum*. Similar screens revealed novel antiparasitic compounds against *Trypanosoma cruzi* and effective inhibitors for *Leishmania major* and *Cryptosporidium parvum*. However, HTS faces challenges such as the need for reliable assays and limited insight into compound mechanisms of action.

3. Structure-Based Drug Design (SBDD) and Fragment-Based Drug Discovery (FBDD)

Structure-Based Drug Design (SBDD) and Fragment-Based Drug Discovery (FBDD) use three-dimensional protein structures to optimize drug candidates. SBDD identified antimalarial compounds targeting dihydroorotate dehydrogenase (DHODH) from *Plasmodium falciparum*. FBDD successfully discovered inhibitors for *Leishmania donovani* N-myristoyltransferase (NMT) and *Trypanosoma cruzi* cruzain. These approaches employ techniques such as X-ray crystallography and NMR (Nuclear magnetic resonance) to facilitate drug design.

4. Omics Sciences

Omics sciences, including genomics, transcriptomics, proteomics, and metabolomics, significantly advance parasitic disease research. Genomics has led to the identification of DHODH inhibitors for malaria. Transcriptomics highlighted upregulated genes in *Leishmania donovani* during infection. Proteomics facilitated the discovery of inhibitors for *Trypanosoma cruzi* cruzain. Metabolomics contributed to identifying inhibitors targeting HDAC8 in *Schistosoma mansoni*, offering critical insights into drug targets and mechanisms.

PHARMACOLOGY IN DRUG DISCOVERY FOR PARASITIC DISEASES

Pharmacology plays a crucial role in drug discovery for parasitic diseases by encompassing both pharmacodynamics, which examines drug effects on parasites, and pharmacokinetics, which

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Published 16/9/2024

studies how drugs are processed by the body.

1. Pharmacodynamics in Parasitic Diseases

Pharmacodynamics is essential for understanding drug effects on various parasitic diseases. In malaria, it helps determine optimal doses and treatment durations for antimalarial drugs and assesses drug resistance and toxicity. For kinetoplastid diseases like Chagas disease, leishmaniasis, and human African trypanosomiasis, pharmacodynamics elucidates how new compounds inhibit essential parasitic enzymes. In helminthic diseases such as schistosomiasis and onchocerciasis, it identifies drugs that disrupt parasite metabolism or target their nervous systems. Ectoparasitic diseases like scabies benefit from pharmacodynamic studies that evaluate the efficacy of drugs targeting cholinergic systems in parasites.

2. Pharmacokinetics in Parasitic Diseases

Pharmacokinetics informs how drugs interact with parasites and are processed by the host. In helminthic diseases, pharmacokinetic studies on drugs like albendazole assess bioavailability and clearance. For ectoparasitic diseases, the pharmacokinetics of ivermectin is crucial for understanding dosing and effectiveness. Pharmacokinetic research also addresses drug behavior in trematodal diseases like schistosomiasis, especially in patients with liver damage, and in cestodal diseases like cysticercosis, guiding dosage and treatment schedules.

Integrating pharmacodynamics and pharmacokinetics enables the development of effective treatments tailored to parasitic diseases, optimizing therapeutic outcomes while minimizing side effects.

RECENT DRUG DISCOVERIES IN PARASITIC DISEASES

Recent advances in drug discovery have led to several promising treatments. In helminthic diseases, new drugs like tribendimidine and emodepside target nicotinic acetylcholine receptors and latrophilin-like receptors, respectively. Oxantel pamoate has been repurposed to treat trichuriasis by inhibiting fumarate reductase in whipworms. Avermectins and praziquantel remain vital for managing onchocerciasis, lymphatic filariasis, and schistosomiasis due to their effects on glutamate-gated chloride channels and calcium influx in parasites.

For ectoparasitic diseases, new classes of drugs such as isoxazolines and spinosyns target receptors in fleas, ticks, mites, and lice. Selamectin, derived from avermectins, offers broad-spectrum activity against fleas, mites, and intestinal worms. Recent discoveries also include novel direct thrombin inhibitors from tick salivary transcriptomes, showing promise as anticoagulants with reduced bleeding risks.

In protozoan diseases, drugs like KAF156 (ganaplacide) and fexinidazole target malaria and human African trypanosomiasis, respectively. LXE408, a novel kinesin inhibitor, is in clinical trials for visceral leishmaniasis. Additionally, clofazimine, a repurposed leprosy drug, is being tested for

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Published 16/9/2024

cryptosporidiosis in children with severe diarrhoea. These advancements represent significant progress in the fight against parasitic diseases and offer new hope for effective treatments.

CONCLUSION:

Drug discovery for parasitic diseases is a multidisciplinary effort that integrates technology, pharmacology, and clinical science, leading to significant progress in developing new treatments. However, challenges like drug resistance, limited resources, and the complex nature of parasites persist. Continued innovation, investment, and collaboration are crucial to eliminating these diseases and enhancing global health.

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