

# Current Advances in Helminth Biology: Bridging Fundamental Discoveries and Practical Applications in Disease Mitigation

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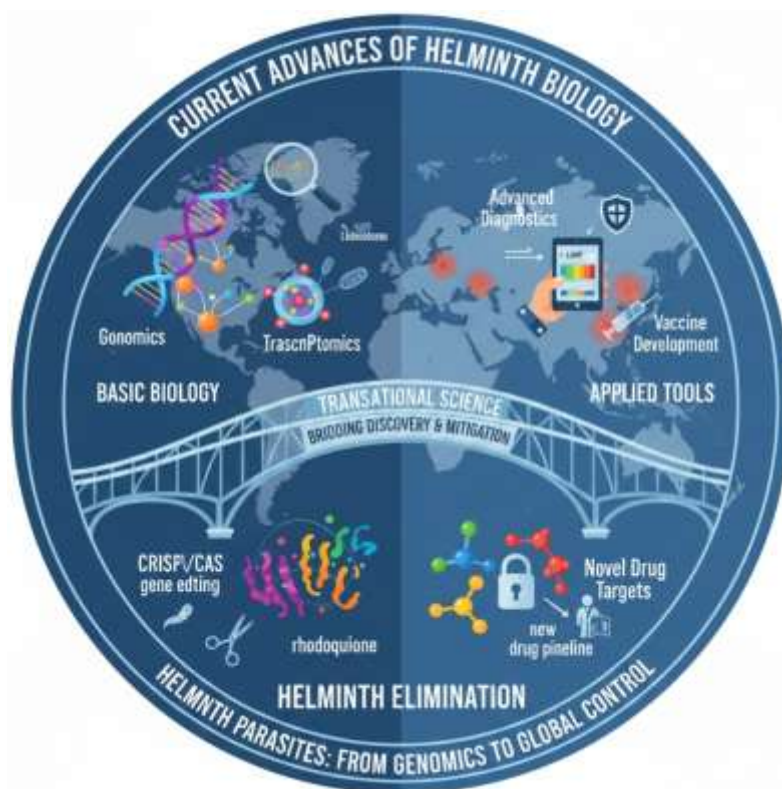
## ABSTRACT

Helminth cestosome infections are linked to neglected tropical diseases (NTDs), which affect over a billion people worldwide and continue to present public health challenges. Although mass chemotherapy has reduced morbidity, the rise of anthelmintic resistance threatens future progress, and effective vaccines are not available, nor are there methods for screening ova (eggs) to detect drug-resistant nematodes. This review, therefore, provides a continuum from basic scientific findings to practical disease-control applications. At the same time, the host-parasite interface and immune system modulation are crucial areas of study. Helminths are skilled at evading the immune system by releasing a complex array of products that inhibit or alter host responses. The structural biology of these Excretory/Secretory (ES) products and their role in parasite function serve two primary purposes: as candidates for new diagnostic tests to identify low-level infections that current methods might miss, and as potential vaccine antigens capable of eliciting protective immunity. This review highlights

recent advances in developing next-generation interventions. We examine the current state of drug pipelines, focusing on compounds targeting nematode-specific molecular pathways and new repurposing opportunities. Additionally, we evaluate progress in PoC diagnostics for surveillance and elimination efforts, emphasizing strategies that utilize circulating parasite DNA/RNA. Lastly, we examine how ecological and spatial modeling, based on fundamental biology including transmission dynamics and larval survival—can help optimize Mass Drug Administration (MDA) for sustainable disease elimination. Overall, the review emphasizes that continued progress against helminthiasis depends on actively translating basic research from parasite genomics and immunology to host-parasite signaling into durable, scalable tools for drug discovery, effective surveillance, and ultimately, long-lasting disease control.

**Keywords:** Helminth Parasites; Basic Biology (or Helminthology); Applied Therapeutics; Omics Technologies (or Genomics); Disease Mitigation (or Drug Resistance)

## Graphical Abstract:



## 1. INTRODUCTION

Helminth infections, caused by nematodes, trematodes, and cestodes, are among the most serious and persistent challenges to global health, agriculture, and animal husbandry. They are mainly classified as Neglected Tropical Diseases (NTDs) by the World Health Organization (WHO), and these long-term, disabling infections affect more than a billion people in low- and middle-income countries. The attendant morbidities, such as malnutrition, stunting, cognitive impairment, anemia, and organ damage (lymphatic filariasis and schistosomiasis), sustain poverty and hinder socioeconomic progress. Although helminthiasis have been linked to lower death rates compared to acute infections (e.g., malaria or HIV/AIDS), the cumulative loss of disability-adjusted life years (DALYs) from chronic parasitic diseases contrasts sharply with a public health burden that is sometimes overlooked. Global control has relied heavily on Mass Drug Administration (MDA) with a limited number of broad-spectrum anti-helminthics, specifically

albendazole and praziquantel. Despite MDA's successes in reducing morbidity, these control efforts have revealed critical programmatic limitations that should redirect the course toward a more scientific approach. The primary issue among these is the increasing problem of anthelmintic resistance [1-2]. Widespread and long-term use of a few drug classes in an often only partially targeted manner exerts strong selection pressure on parasite populations. although it is notoriously difficult to definitively establish the existence of drug resistance in human helminths, there are plenty of warnings from veterinary helminthology (where resistance of worms to drugs is widespread and often severe) for the health sector. Additionally, relying on drugs that only partially reduce worms' activity leads to the continued transmission of low-intensity infections, which further worsen and complicate elimination efforts. A second limitation is in Diagnosis and monitoring. The current Diagnosis of intestinal helminth infections using the Kato-Katz method, the Gold standard, relies on microscopy and

requires trained personnel and basic infrastructure. This limitation hampers elimination programs by preventing the identification of the true remaining foci of infection that sustain transmission [3-4].

The final stated troubles leave no doubt that simply the "physiological top-down" treatment by medication has reached a saturation point. A deeper understanding of the basic biology of these parasites is urgently needed to meet the ambitious targets for sustained control and eventual elimination of helminthiases. Basic science in helminthology is not just a nice academic exercise; it is the foundation that underpins the discovery of new interventions to escape resistance. Knowledge of these species-specific metabolic and gene networks, as well as the molecular complexity of their surface molecules and secretions, is crucial for identifying new targets for drug intervention. For example, detailed characterization of an enzyme essential for egg production in *Schistosoma* or of a particular ion channel vital for nematode movement provides a molecular "Achilles heel" that remains resistant to existing classes of drugs. It is this need for new science that defines the central aim of this review: to examine and investigate the translational pipeline from discoveries in fundamental helminth biology to practical applications for disease reduction. We aim to connect the 'bench,' where genomic data and molecular mechanisms are discovered, with the 'bedside' or 'field,' where new diagnostics, effective vaccines, and resistance-proof drugs are urgently needed. This synthesis will demonstrate how recent technological improvements, especially in 'omics' technologies (genomics, transcriptomics, proteomics) and immunology, are driving this change. This manuscript aims to do exactly that by systematically reviewing the latest developments in basic science and applying them directly to the development of new drugs that will diagnose, prevent, or treat helminth infections. This approach aims to underpin innovative control strategies and establish a vital framework for prioritizing

research efforts with significant potential to advance the global control and elimination agenda beyond current achievements. The era of reliance solely on 20th-century drugs must now give way to a new era based on detailed molecular architecture and analysis of the helminth parasite [5-6].

## **2. Unraveling the Helminth Blueprint: Advances in Molecular and Functional Biology Focus**

The post-genomic era has shifted research on helminth parasites from basic anatomical observations to detailed visualization of their complex molecular machinery. This in-depth exploration of genomics, transcriptomics, proteomics, and metabolomics is essential for the targeted identification of new drug targets and intervention points that bypass the pathways used by, or affected by, increasingly ineffective traditional anthelmintics. The completion of reference genomes for major human helminths, such as *Schistosoma mansoni*, *Brugia malayi*, and several hookworms, has served as a "blueprint" that enables a deeper understanding of their biology. These datasets have implications for rapid discovery through comparative genomics of parasite-specific genes that are either absent or nearly identical to human functional homologs. These unusual genes are generally crucial for the organism's survival, making them high-priority, high-confidence new-drug targets because their inhibition is expected to cause little to no off-target host toxicity [7-8].

In addition to the static genome, transcriptomics (the study of RNA transcripts) is crucial for understanding the parasite's dynamic behavior. Helminths also have complex life cycles that may involve a variety of host environments and extreme developmental changes (e.g., from free-living larva to parasitic adult). Transcriptomic analyses, such as single-cell RNA sequencing (scRNA-seq), show the particular genes and gene regulatory networks (GRNs) that are turned on or off at each step from larval invasion to adult

reproduction. Focusing on stage-specific targets, such as genes that control egg production in adult females or the transition to an infective larval stage, could enable treatments that sterilize the parasite or prevent it from passing to others, rather than simply killing the adult worm. There are also many genes that change their expression (e.g., upregulate drug efflux pumps or mutate the target protein) in response to selective anthelmintic pressure and allow resistant strains to survive drug treatment – so transcriptomics is incredibly useful for this type of work [9-10].

### **2.1. Proteomics and Metabolomics:**

#### **Delineating the Achilles' Heels**

Whereas genomics tells us what can be made, proteomics and metabolomics (the study of all proteins and small-molecule metabolites) inform us which products the parasite is actually making to survive in the hostile environment of its host. Proteomics is particularly important in the characterization of Excretory/Secretory (ES) products. They are the cocktails of proteins and small molecules produced as helminths spray out into host tissue. ES products constitute the parasite's biochemistry for digesting host tissue, evading host immunomodulation, and regulating nutrient uptake. The key enzymes and structural proteins in this proteome can not only be targeted, but also serve as candidate targets for next-generation vaccines and very specific diagnostics. Metabolomics is a functional map of the parasite's energy and nutrient requirements [11-12]. Because they inhabit anoxic sites such as the gut or bile ducts, helminths have developed specialized machinery for energy production. A notable exception is the incorporation of the atypical electron carrier, rhodoquinone (RQ), in anaerobic respiration by many parasitic nematodes. Since the RQ biosynthetic pathway does not occur in the human host, enzymes responsible for its synthesis are extremely attractive, low-risk drug targets, the very bottleneck of metabolism. The identification and molecular characterization of these parasite-specific metabolic enzymes provide direct

targets for structure-based design of species-selective small-molecule inhibitors. Functional validation of a novel drug target is essential if we wish to modulate the parasite's genes. Functional genomics: Functional genomic approaches, and in particular the recycling of technologies such as RNA interference (RNAi) for some helminths and the recent advent of CRISPR/Cas9 gene editing for others (especially *Schistosoma mansoni* and selected species of Strongyloides), have been game-changers [12-13].

These tools let scientists turn off or edit a target gene and see how this affects the parasite's viability, development, or reproductive ability. This is a critical step in validating that a candidate gene is indispensable for the parasite's survival. In addition, applying these tools in developmental biology is revealing the mechanisms by which complex life cycle stages, such as the transition from a non-infective stage to a host-penetrating larva, are regulated. Preventing the parasite from ever reaching its adult, reproductive stage (a disruption of these developmental checkpoints) is therefore a promising strategy that would lead to avoidance of pathology and transmission. That is, the combined might of these molecular disciplines yields a fine-grained genome map of helminth weaknesses that forms the platform on which all subsequent applied science and disease intervention strategies must be erected [14-15].

### **3. Translating Discovery into Action: Novel Tools for Helminth Disease Mitigation**

The endpoint of effective basic research is the deployment of an applied tool that directly benefits public health. The molecular and immunological insights derived from the parasite's plan are now being systematically manoeuvred into three key areas: new drug development, highly sensitive diagnostics, and data-driven refinement of control programme delivery methods. This applied translational emphasis is necessary to break

the cycle of depending on MDA and promoting elimination targets that are unattainable [16].

### **3.1. New Anthelmintic Drug Development in the Pipeline**

New anthelmintics are urgently required due to limitations of current drugs and the potential for resistance, which has led to a paradigm shift in drug discovery from circumstance discovery towards rational design. This richness of genomic and proteomic information has facilitated the recent emergence of phenotypic screening for activity against whole parasites in chemical libraries, thereby identifying compounds active against resistant strains. Various promising compounds, frequently discovered through drug repurposing (screening approved non-anthelmintics, e.g., insecticides such as tolfenpyrad for anti-helminth activity), are advancing into pre-clinical and clinical trials. Importantly, the emphasis is now on more than just a reduction in worm burden to identifying parasite-resistance pathways. For example, delivery of gene silencing RNA to the pharynx in *C. elegans* results in disruption of the worms without harming the host (4), while unique characteristics such as rhodoquinone biosynthesis pathway present only in nematodes and specific ion channels including nicotinic acetylcholine receptors that are different from their corresponding host targets are also being implicated as low risk, high specificity targets (5). Moreover, innovation of treatment strategies that combine drugs with distinct mechanisms to arrest resistance emergence and attain higher cure rates, especially for recalcitrant species such as *T. trichiura*, is being investigated [17-18].

### **3.2. New Developments in Diagnostic Coverage: Surveillance and Accuracy**

A game-changer in a programmatic sense is the shift from low-sensitivity, labor-intensive microscopy (such as Kato-Katz methods) to highly sensitive molecular diagnostics. The core science behind these advances, by sequencing helminth genomes and identifying species-specific gene regions

(e.g., ITS-1, 18S rRNA), supports qPCR assay development. qPCR is a multiplex technique that enables the simultaneous detection and quantification of DNA from multiple parasite species in a single sample (e.g., stool). This breakthrough is significant for surveillance in low-endemic areas where infections are mild and can be missed by microscopy, as well as for monitoring the impact of MDA programs. In resource-limited settings, the field is exploring ways to make these tools more affordable, and coverage technologies such as Loop-Mediated Isothermal Amplification (LAMP) are being considered. LAMP amplifies DNA at a constant single temperature with high efficiency and without the need for expensive thermocyclers. These approaches can be developed into Point-of-Care (PoC) forms, often applying visual detection (e.g., turbidity or color change) and requiring low expertise. Meanwhile, there is an emphasis on developing non-invasive molecular assays that detect circulating parasite antigens or nucleic acids in urine or blood (which are very useful for systemic infections such as schistosomiasis and lymphatic filariasis) [18-19].

### **3.3. Optimal Control Strategies: Modeling and Geostatistics**

In recent years, plotting infection sources, spatial modeling, and predictive surveillance have played an increasingly important role in developing optimal control strategies. Using biological data—such as "0D"-Model reproductive rate of the parasite, drug efficacy, and egg half-life in the environment—and environmental factors like climate, land cover, and proximity to water bodies, a method called Bayesian geostatistical model-based ridge regression was employed and then interpreted to create high-resolution risk maps. These maps offer precise predictions of infection prevalence and intensity in areas that haven't been surveyed. They also enable NTD national control programs to shift from MDA (mass drug administration) campaigns to a more targeted strategy, focusing resources specifically on local sub-populations or

geographic "hot spots" at highest risk or critical for maintaining transmission. Furthermore, complex transmission dynamics models are used to forecast elimination progress, estimate the number of treatment rounds needed, and determine the most effective combination of interventions (e.g., MDA along with WASH: Water, Sanitation, Hygiene measures). Integration of such predictive data with real-time molecular surveillance will help control programs move beyond reducing morbidity toward an effective and sustainable path toward elimination [19-20].

#### 4. CONCLUSION

Our broad overview of recent developments in helminth biology underscores the need for a strong commitment to translational science to achieve global goals for sustainable control and eventual eradication of helminth infections. Control programs have traditionally depended on a limited and aging set of anthelmintic drugs, a practice increasingly challenged by the rise of resistance to chemical treatments and the limited sensitivity of traditional diagnostics. The detailed and high-resolution insights provided by omics technologies (genomics, transcriptomics, and metabolomics) have been crucial in identifying the worm's vulnerabilities at a molecular and metabolic level. These findings are universal and fundamental to the parasite's biology, and they are not merely theoretical; they directly inform the development pipeline by offering models for designing new therapeutics targeting parasite-specific pathways. This strategy offers advantages like reducing host toxicity and avoiding existing resistance. Additionally, a better understanding of host-parasite communication and immune modulation is speeding up the creation of next-generation, highly specific diagnostics and vaccines, which are currently of the highest priority.

And importantly, the translation of discovery into action is now being redirected to focus on public health delivery itself. Molecular assays, such as LAMP, are being developed

into point-of-care (PoC) modalities for surveillance in resource-limited settings. At the same time, computational models (of spatial dynamics and transmission) based on accurate biological data are opening new avenues away from generic MDA towards targeted intervention. This evidence-based approach enables efficient use of limited resources and is crucial for eliminating remaining infection hotspots to break transmission. In conclusion, the strategy for helminth control has fundamentally changed. The momentum must be sustained through ongoing significant investment in basic helminthology to continue expanding our pipeline of diverse targets and a strong commitment to translating new discoveries from the lab into reliable, scalable tools. If a dependable bridge between bench and bedside can be established to close this gap, the scientific community could go beyond merely controlling morbidity associated with helminthiasis and ultimately achieve the goal of global eradication.

#### *Declaration by Authors*

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