



Opinion

Single-cell Transcriptomics and Antibody Immunotherapy: A Potential Dual Strategy against Antimalarial Drug Resistance



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Malaria remains a serious global health challenge, with 282 million cases and 610,000 deaths in 2024.¹ Despite gains from artemisinin-based combination therapies, drug resistance remains a major challenge in malaria control efforts and elimination,^{2,3} with Egypt certified malaria-free by WHO in 2024.¹ Notably, genetic mutations, epigenetic and transcriptional regulation contribute to antimalarial drug resistance.⁴ Key gene mutation-related resistance mechanisms include PfK13 mutations for artemisinin, PfCRT/PfMDR1 mutations for chloroquine, and PfDHFR/PfDHPS mutations for sulfadoxine-pyrimethamine.^{2,5}

Antimalarial pipelines can face challenges as *Plasmodium falciparum* and related *Plasmodium* species may adapt through several forms of plasticity, such as stage-specific expression programs and epigenetic switching without gene mutations.

Single-cell transcriptomics may help identify parasite evasion mechanisms and could inform future antibody immunotherapy strategies targeting parasite subpopulations and conserved epitopes. In this conceptual framework, candidate antigens associated with drug-tolerant or persistent parasite states would require independent validation for surface exposure and antibody accessibility before antibody-based targeting. The proposed approach could potentially help suppress resistant clones and address potential mechanisms of escape associated with drug-resistance genes,⁶ particularly if such validated targets are associated with drug-tolerant or persistent parasite subpopulations. This would not eliminate drug resistance but could potentially help mitigate its emergence by reducing the survival of such subpopulations under drug pressure. This proposed strategy may complement approaches targeting metabolic resistance pathways.

Potential benefits could include reducing recrudescence and blocking transmission-specific stages.

Broad-acting antimalarials can target multiple parasite life-cycle stages,⁷ while transcriptional and epigenetic plasticity may contribute to parasite survival under drug pressure.⁴ This dual

approach could potentially help prolong drug lifespan and limit the emergence of resistance. Sustained epidemiological surveillance of parasite mutant antigen diversity is valuable to support this.

A coordinated framework could combine single-cell RNA sequencing (scRNA-seq) to map transcriptional heterogeneity and identify stage-specific vulnerabilities with antibody immunotherapy informed by these transcriptomic insights, as proposed here as a potential dual-front strategy. Molecular therapeutics for malaria may benefit from this approach.

This Opinion outlines key concepts in the heterogeneity-resolving ability of single-cell transcriptomics, linking these insights to guided antibody immunotherapy, and proposes their integration into an intervention that represents a novel conceptual framework for future therapeutic strategies against antimalarial drug resistance.

Stage-specific transcription programs may vary across merozoite invasion, intraerythrocytic growth, and gametocyte transmission.⁸ This approach considers transcriptional states, not just proteins or static mutations, and is conceptually intended to help identify vulnerabilities relevant to resistance.⁴ Single-cell transcriptomics can help resolve this heterogeneity. By profiling individual parasite cells using single-cell transcriptomics across the parasite life cycle, researchers can identify which gene expression programs are active under drug pressure.⁴ Recent scRNA-seq datasets reveal stage-specific gene expression patterns across the *Plasmodium* life cycle.⁸ This includes bifunctional PfDHFR-TS (gene ID Pf3D7_0417200), which is critical for folate and nucleotide biosynthesis and has been identified in a sexual-stage scRNA-seq dataset.⁹ Other targets include Pf3D7_0316800, a 40S ribosomal protein S15A involved in protein synthesis.⁹ These are cell-level expression patterns that may be obscured in bulk RNA-seq.¹⁰

Antibodies are part of humoral immunity and synergize with cellular immunity. Monoclonal antibodies and nanobodies, the latter being ultrasmall antibody fragments with high stability and strong binding affinity, have been explored for malaria prevention.

Most malaria monoclonal antibodies are designed to prevent infection rather than overcome established drug resistance. Prophylactic or preventive antibody immunotherapy (passive immunoprophylaxis) is given before infection or before symptoms

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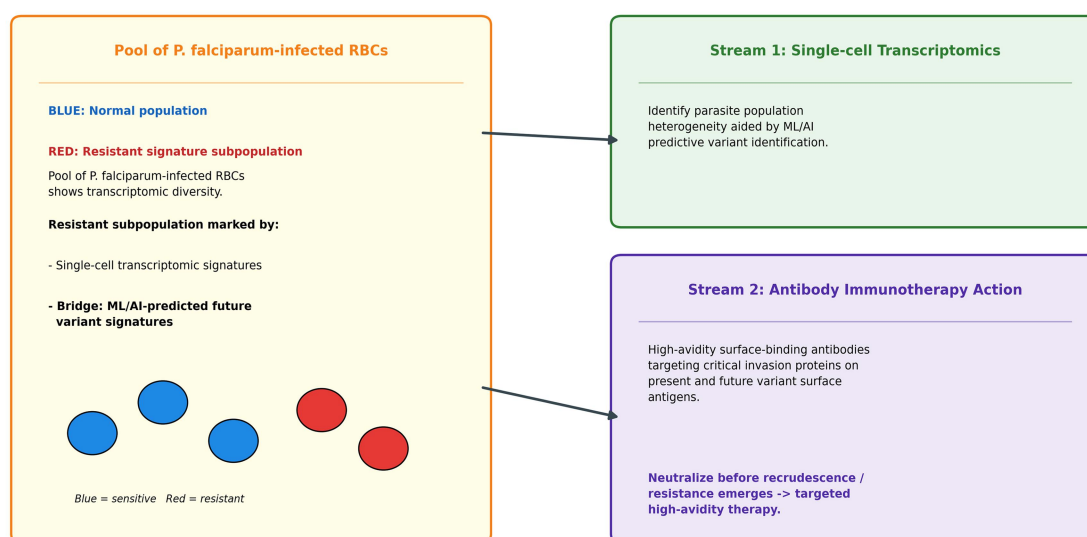


Fig. 1. Mechanistic synergistic streams of ML/AI variants predictive power-aided single cell transcriptomics and antibody immunotherapy at host-parasite interface to tackle *Plasmodium* drug resistance. AI, artificial intelligence; ML, machine learning; RBC, red blood cell.

develop to reduce the risk of infection or disease. Separately, the malaria vaccines RTS, S/AS01 and R21/Matrix-M were recommended by WHO in October 2021 and October 2023, respectively.¹¹

Therapeutic or curative antibody therapy (passive immunotherapy) is given after infection or after symptom onset to treat established infection. Antibody therapies may be used for either prevention or treatment, and both applications involve distinct clinical goals. Examples include monoclonal antibody therapy for Ebola and the use of rabies immunoglobulin for rabies.^{12,13} For malaria, monoclonal antibodies such as CIS43LS are under clinical investigation primarily as prophylactic interventions rather than as treatments for established infection.¹⁴

While single-cell transcriptomics is a discovery tool, when used in infectious disease research, it may help identify stage-specific expression states and candidate antigens that could inform antibody studies, while structural analyses can characterize determinants of antibody binding and genomic analyses can identify potential escape variants emerging during persistent infection (Fig. 1).^{15,16} Related genomic approaches have also been used to investigate viral variants associated with antibody escape in infectious diseases such as COVID-19.

Transcriptomic maps may guide the discovery of future small-molecule targets. For instance, M5717, a *Plasmodium* eukaryotic translation elongation factor 2 inhibitor evaluated as a small-molecule antimalarial, has shown preclinical evidence of parasite clearance when combined with pyronaridine.¹⁷ Its identification is not attributed to single-cell transcriptomics. This distinction clarifies that single-cell transcriptomics may help prioritize translation-related vulnerabilities, while other approaches are required to develop and deliver corresponding interventions.

Mutations in pathogen proteins can confer antibody resistance when they result in reduced susceptibility to the parental antibody. Selecting for such mutants resistant to the particular parent

antibody in cell culture is an established approach for studying antibody resistance,¹⁸ while antibody-driven escape variants have also been observed during persistent infection.¹⁶

Therefore, designing antibodies to target such proteins could, in principle, support the development of more escape-resistant therapeutic antibodies. The central concept proposed here is that antibody strategies might be combined with single-cell transcriptomics mapping of candidate proteins and variants to reduce the potential for parasite escape. This could represent a future therapeutic strategy, but it requires experimental and clinical validation.

Conventional drug pipelines have not failed; they have adapted and continue to deliver. Artemisinin combination therapy and emerging combinations such as ganaplacide-lumefantrine remain essential. Single-cell transcriptomics complements rather than replaces these approaches by adding resolution to parasite transcriptional plasticity that may be associated with tolerance and transmission. Future antibodies tailored to validated parasite antigens could potentially contribute to parasite inhibition, pending further validation.¹⁹

Barriers that block translation to human health include cost and access. Protection from some monoclonal antibodies can last for months,¹⁴ However, dosing, delivery, data integration challenges, the complexity of translating transcriptomic signatures into clinically actionable therapeutic targets, and affordability may limit their use in low-income countries where the burden is highest.²⁰ Single-cell transcriptomic analyses may also be affected by sampling and cell-recovery biases, which can influence the apparent representation of parasite stages and transcriptional states.

Key proteins highlighted by single-cell transcriptomic studies require independent experimental, pharmacological, and clinical validation before they can be considered druggable targets. Addressing these challenges will require human-focused optimization, such as the application of optimized dose regimens, delivery

routes, and formulations informed by human pharmacokinetics. Single-cell transcriptomics is a discovery and profiling method, not itself a treatment. Its power lies in decoding stage-specific transcription and cellular heterogeneity in *Plasmodium* parasites and identifying relevant states and candidates.

Nanobodies could be considered “precision antibodies” when their targets are selected using identified variant information from single-cell transcriptomics. Transcriptomics could be used to identify antigens highly expressed during vulnerable stages or in drug-resistant subpopulations. Generally, future antibodies could be bioengineered using target-selection strategies informed by large single-cell transcriptomic datasets, together with predictive tools such as machine learning and artificial intelligence to identify antigens or molecular targets with a high likelihood of developing resistance-associated alterations. Such approaches could better guide the selection and use of appropriate neutralizing antibodies before resistance emerges (Fig. 1).

Single-cell transcriptomics decodes stage-specific gene expression, transcriptional heterogeneity, and parasite adaptation. Antibody immunotherapy informed by such transcriptomic maps could support more precise interventions. Genetic mutations (such as PfK13, PfCRT, PfMDR1, PfDHFR, and PfDHPS) remain central to resistance, while transcriptional adaptation may provide additional layers of regulation that single-cell transcriptomics may help illuminate. Single-cell transcriptomics may help identify parasite-stage vulnerabilities and guide future target discovery, while antibody-based prevention and other precision interventions require further validation for affordability, delivery, durability, and clinical impact.

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Conflict of interest

The author declares no conflict of interest.

Author contributions

LN Ozurumba-Dwight is the sole author of the manuscript.

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